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IDENTIFYING AND CONTROLLING POISONS OF THE NERVOUS SYSTEM

HEARING

BEFORE THE

SUBCOMMITTEE ON
TOXIC SUBSTANCES, ENVIRONMENTAL OVERSIGHT,
RESEARCH AND DEVELOPMENT

OF THE

COMMITTEE ON
ENVIRONMENT AND PUBLIC WORKS
UNITED STATES SENATE

ONE HUNDRED FIRST CONGRESS

SECOND SESSION

ON

THE OFFICE OF TECHNOLOGY'S REPORT ENTITLED "NEUROTOXICITY: IDENTIFYING AND CONTROLLING POISONS OF THE NERVOUS SYSTEM" AND RELATED RESEARCH AND REGULATORY ISSUES

OCTOBER 3, 1990

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IDENTIFYING AND CONTROLLING POISONS OF THE NERVOUS SYSTEM

WEDNESDAY, OCTOBER 3, 1990

U.S. SENATE,
COMMITTEE ON ENVIRONMENT AND PUBLIC WORKS,
SUBCOMMITTEE ON TOXIC SUBSTANCES,
ENVIRONMENTAL OVERSIGHT, RESEARCH AND DEVELOPMENT,
Washington, DC.

The committee met, pursuant to notice, at 9:34 a.m., in room 406, Dirksen Senate Office Building, Hon. Harry Reid (chairman of the subcommittee) presiding.

Present: Senators Reid, Warner, Lieberman, and Jeffords.

OPENING STATEMENT OF HON. HARRY REID, U.S. SENATOR FROM THE STATE OF NEVADA

Senator REID. The Subcommittee will come to order.

Today the Subcommittee will receive testimony on a subject that may affect each of us to an unknown and unpredictable degree in our lifetimes, some impact, either temporary or permanent, to our nervous systems from exposure to a chemical, a food additive, or even a medication.

Dramatic incidences of poisoning from neurotoxic substances are all too frequent in our history. During the days of prohibition, an outbreak of partial paralysis occurred known as Ginger-Jake Syndrome. Originally sold as an all-purpose ginger-based medical tonic, bootleggers learned to produce an adulterated version for sale as illegal liquor. One bootlegger substituted lyndol for the more common adulterants, molasses or castor oil, which were used to deceive Federal inspectors who periodically tested the content of the tonic.

Lyndol, used in lacquers and varnishes, contained a chemical known as TLCP. The chemical produced symptoms from temporary numbness to permanent paralysis in an estimated 20 to even 100,000 victims before supplies were seized.

In 1979, workers at a bathtub manufacturing plant in Texas began to experience neurological problems, including dizziness and memory loss, within weeks of the introduction of a compound containing BHMH, used in the production of reinforced plastics. Though use of the compound was suspended, symptoms persisted in some of the workers two years later. Preliminary tests have demonstrated neurotoxicity of BHMH, but no regulatory action had been taken before the compound was marketed.

These were two incidents of many described in a landmark report released by the Office of Technology Assessment in May. The report chronicles what we know about neurotoxicity, but more importantly it chronicles what we don't know about neurotoxicity. We're meeting this morning to receive testimony from experts in the field and to learn what directions we need to take to assure a better Federal response.

Neurotoxicity has been a factor in many of the issues the Subcommittee has reviewed over the past two years. We've heard firsthand the testimony of those that have suffered neurological impairment through exposure to chemicals in the work place. We've also heard from those who have suffered from exposure to household, lawn, and agricultural pesticides. Most recently, we have learned about the debilitating effects lead can have on children.

Chemicals pervade every aspect of our lives, regardless of occupation, locale, or social status, but there is a down side to all the benefits of chemicals in our modern-day society, a down side too dangerous to overlook: the unestimated toll that chemicals may be taking overall on our public health.

One of the primary gate keeper laws to protect the public and the environment from harmful chemicals is the Toxic Substances Control Act, or TSCA. An objective this morning is to see how well TSCA authorities are working with respect to controlling neurotoxic chemicals. We'll hear discussion of the Federal Insecticide, Fungicide, and Rodenticide Act, better known as FIFRA, and what is being done to protect workers and the public from neurotoxic pesticides.

As the OTA report points out, there are 65,000 chemicals on EPA's inventory, and some 1,500 notices of new chemicals are received each year. Yet, little is known about the neurotoxic properties of the 65,000, and of course the 1,500 each year.

Chemical manufacturers should be required to do a more thorough job of toxicity testing to give EPA a better basis for making regulatory decisions. EPA is often asked to pass judgment on new chemicals with little or no information about its risks. The burden of proof should be shifted to industry to prove the safety of chemicals, rather than EPA.

There is much to be done in the research area. Development of less expensive and faster screening tests is a linchpin in getting more information about suspected neurotoxic chemicals. We will look specifically at EPA's neurotoxicity research program today. We will also begin an information campaign on neurotoxicity, which will guide us in the consideration of legislation to safeguard the public.

The testimony presented today will give us a basis that will be useful as the Subcommittee pursues research issues and considers amendment to TSCA in the coming year.

OPENING STATEMENT OF HON. JOHN W. WARNER, U.S. SENATOR FROM THE COMMONWEALTH OF VIRGINIA

Senator REID. Senator Warner.

Senator WARNER. Thank you, Mr. Chairman. I'll include my statement in the record.

Senator REID. Without objection, that is the order.

Senator WARNER. I would like to make one point, though. We have no in-house capability to produce, create, and bring together the highly technical nature of this subject, therefore we have to rely very heavily on the expert witnesses that we will hear from today and perhaps at a later session. So it's incumbent on us to accept this testimony in a very cautious way. I hope that we will be unbiased and objective as we make the tough decisions. Those decisions will be largely predicated on the information from the technical people who come forward.

Mr. Chairman, I also note that this is probably the last hearing of this Subcommittee prior to the conclusion of this Congress. I join other colleagues on this Committee and the Senate in saying to you, as we say it in the Navy, "A Navy well done" for your chairmanship. This is your first term here. And I look forward to the coming years—assuming November goes reasonably well for me—to rejoining you next year.

Good luck.

[Senator Warner's statement follows:]

OPENING STATEMENT OF HON. JOHN W. WARNER, U.S. SENATOR FROM THE COMMONWEALTH OF VIRGINIA

Mr. Chairman, I want to thank you for convening today's hearing on the very serious subject of neurotoxicity, or the effect of chemicals on the functioning of the nervous system. Today's hearing continues this Subcommittee's inquiry into a subject of great interest to both the Chairman and myself: the effect of the ever-increasing numbers of chemicals on our daily lives.

Today, the Subcommittee will hear a discussion of the results of a report of the Office of Technology Assessment on the problems associated with identifying and controlling neurotoxicity. In addition, we will hear a report from EPA on their activity in this area, both through regulation and research. Finally, we will hear from researchers working on the front lines to gain a better understanding of the effects of human exposure ot toxic substances.

Mr. Chairman, many of the policy decisions made by this Committee, indeed most of them, necessarily rely heavily on the scientific evidence provided to us by experts. For that reason, it is incumbent on us to ensure that scientific research is as thorough and reliable as possible. I will listen to the testimony today, in hopes that the witnesses can recommend ways for us to achieve this goal in the area of neurotoxicity.

I welcome the witnesses and look forward to their testimony today.

Thank you, Mr. Chairman.

Senator REID. Thank you very much, Senator Warner.

OPENING STATEMENT OF HON. JOSEPH I. LIEBERMAN, U.S. SENATOR FROM THE STATE OF CONNECTICUT

Senator Lieberman.

Senator LIEBERMAN. Mr. Chairman, I echo those words. I want to say, first of all—while the sounds are still lingering—I only hope that I face November of 1994 in the same condition that Senator Warner faces this November. It would be one of my fondest prayers, and deservedly so, for Senator Warner certainly.

This is my first term so I don't have much to compare it to, but serving on this Subcommittee has been an extraordinary experience for me. I don't know of anything more satisfying than the work that I've done in this Subcommittee and of working with you, Mr. Chairman, and the ranking republican member, Senator Warner. I think we've really broken some new ground, accom-

plished things, and begun to do some other things that we know we have to follow up on in the coming session.

So I join in this salute and I extend it to Senator Warner, as well, who has been so critical in the successes that we've had.

I thank you for convening this hearing today. I have a statement that I would like to be included in the record. It honestly echoes much of what you said, Mr. Chairman. I think the basic point here is that we're trying to gauge accurately the impact of the chemicals, that we've all come to depend on in many ways, on our health.

We understand particularly, from the OTA report, that while we've been focused on the carcinogenic effects—the cancer-causing effects—of these chemicals, the neurotoxic effects, as the OTA report said, may pose an equal or greater threat to public health. We saw it in the case of lead poisoning, with the impact of the studies that showed an extraordinarily negative impact on the brain functioning of children in this Country. So this is the next area for us to try to help lead in.

I remember in May of 1989, which is almost about a year and half ago, Doctor Wood, who is testifying here today, was before us and he stressed the vulnerability of our children to neurotoxic substances and urged that EPA adopt testing procedures for neurotoxic screening of those chemicals. For the last year and half, EPA has been telling us that it is working on those guidelines. I think they're critical, and I look forward to the testimony today from EPA on that subject, as I do testimony of all the witnesses.

Thank you, Mr. Chairman.

[Senator Lieberman's statement follows:]

OPENING STATEMENT OF HON. JOSEPH I. LIEBERMAN, U.S. SENATOR FROM THE STATE OF CONNECTICUT

Mr. Chairman, I am pleased that you have convened this hearing on neurotoxicity. In the almost two years that I have served on this Subcommittee with you, the issue of the neurotoxic effects of chemicals used in our society today has come up in every hearing I have participated in. Time and again we have heard that the government was not adequately reviewing the possible neurotoxic effects of chemicals and was not acting swiftly enough to protect Americans from known neurotoxic substances. The report issued by OTA this spring confirms much of what we have heard at hearings on food-use pesticides, lawn care pesticides, and lead. I hope that now that the problem has been acknowledged, we can today discuss what the Federal Government should be doing to protect both children and adults from neurotoxic substances.

In the hearings this Subcommittee has held on lawn chemicals and lead, we heard extensive testimony about the potentially devastating neurotoxic effects of common pesticides which are routinely used on our lawns and gardens and of lead which is used extensively throughout our society. It was evident from those hearings that while the Federal Government and consumers have been focused on the potential carcinogenic effects of toxic substances, we have neglected neurotoxic risks which as the OTA report states "may pose an equal or greater threat to public health." Exposure to neurotoxic substances may affect children every remaining day of their lives. As we have seen with lead, exposure to a toxic substances can affect a child's ability to learn, to communicate, and to function in our society. The harms we risk and the costs we incur by exposing pregnant women and growing children to neurotoxic substances are enormous and should prompt us to spend more resources to ensure that they are not exposed to these substances.

In May of 1989, almost a year and half ago, we heard testimony from Dr. Ron Wood, who is testifying here again today, about the need to test pesticides and their inert ingredients for neurotoxicity. Dr. Wood stressed the vulnerability of children to neurotoxic substances as well as the risks to which workers who manufacture,

mix, and apply chemicals are exposed daily. He urged that EPA adopt testing procedures for neurotoxic screening of the chemicals it reviews. EPA has been telling us for the past year and a half that the Agency is working on neurotoxicity testing guidelines. We eagerly await these guidelines and look forward to getting an update from EPA today on the status of these guidelines as well as on how these guidelines will address concerns about developmental neurotoxic effects and about neurotoxic effects on children and on workers who are exposed to neurotoxic substances in the course of their employment.

There are more than 65,000 chemicals in EPA's inventory of toxic substances, yet only a very few have been tested for neurotoxic effects. We must begin an aggressive process of review to determine which of those pose risks to us and to our children. We must also focus resources on research into neurotoxic effects and on the development of better, more accurate, more efficient testing methods. We can no longer ignore the risks of neurotoxic substances, particularly the risks they pose to our children. I hope that the OTA report will prompt much needed action by the government agencies responsible for reviewing potentially neurotoxic substances.

Senator REID. Thank you, Senator Lieberman.

The first panel today will consist of Doctor Peter S. Spencer—we'd ask you to come forward, please—who is from Portland, Oregon, the Chairman of the New Developments in Neuroscience Advisory Panel; and Doctor Mark Schaefer, the Project Director on the report that we have talked about here today. Doctor Schaefer is from the Office of Technology Assessment.

We would ask that you limit your remarks to five minutes, if you could, to leave ample time for the panel to direct questions to you.

Doctor Spencer.

STATEMENT OF PETER S. SPENCER, CHAIR, NEW DEVELOPMENTS IN NEUROSCIENCE ADVISORY PANEL, OREGON HEALTH SCIENCES UNIVERSITY

Dr. SPENCER. Senator Reid, Senator Lieberman, and Senator Warner: industrial solvents and pesticides that cause muscle paralysis and loss of sensation in workers—lead-based paints that damage children's brains, behavioral and functional changes linked to therapeutic and abused drugs—these are a few of the many disorders of the human nervous system that follow overexposure to chemical substances with neurotoxic potential.

Scientific study of this problem is in its infancy. Only the most obvious connections between chemical cause and neurotoxic effect have been made. New evidence has revealed causal links between chemicals and major neurological and psychiatric disorders including spasticity, parkinsonism, and dementia. There is also a compelling recent association between environmental agents and diseases resembling Lou Gehrig's disease and Alzheimer's disease.

We now suspect that adverse health effects of certain chemicals may remain silent for months, years, or even decades prior to the appearance of fatal brain disease. This principle is well established for chemical triggers of cancer, but it is quite new—in fact, it's a revolution—in neurology.

There is no surprise that the brain—the most important organ in the human body—is peculiarly vulnerable to the effects of foreign substances. Because the nervous system allows us to breath, see, hear, feel, walk, think, and express emotion, and because chemical substances may disrupt all these and many other critical body functions, the possible variety of adverse health effects is huge.

Unfortunately, few scientists are working on the crucially important subject of linking chemicals with neurobehavioral dysfunction, and there is a great need to increase research and to increase training in neurotoxicology. An investment of this type will predictably lead to the identification of more causal links between occupational/environmental chemicals and neurological/behavioral disorders.

This will provide a solid scientific basis not only to design methods for improved treatment but also to implement disease prevention. Imagine the long-term cost savings in health care if Parkinson's or Alzheimer's disease, like smallpox, could be controlled and eventually eradicated.

While neurotoxic chemicals pose a threat to normal human behavior and function, they also provide an invaluable experimental tool for biomedical scientists. Because selected chemicals are able to reproduce in test systems many of the manifestations of human diseases of unknown cause, researchers often employ toxic chemicals to prove brain function in normal and abnormal states. In the past 10 years, over 500 papers have been written on a chemical called MPTP that caused parkinsonism in American drug addicts and thus became a tool to investigate Parkinson's disease. We now know that there is a whole class of such dangerous chemicals, some of which have been used—perhaps surprisingly—by neurotoxicologists to design an effective therapy to retard the course of this disease.

Chemicals with potential to damage the nervous system and alter behavior have sometimes turned up where they are least expected. Substances approved for use as food additives, health foods, fragrance raw materials, and anti-dandruff shampoos—all of which are in use today—have been shown in animals to induce irritability, seizures, and brain or nerve damage. Their effects in humans are unknown and uninvestigated.

Other chemicals have entered commerce with little or no premarket screening for neurotoxicity. Impaired vision, partial paralysis, bladder dysfunction, and personality change have been some of the tragic consequences among exposed workers. Even therapeutic drugs taken in prescribed amounts not uncommonly result in long-term disability. Witness the disabling movement disorders resulting from prolonged treatment with L–DOPA or major tranquilizers. A promising new experimental drug to fight AIDS is limited by its painful neurotoxic effect.

These examples illustrate graphically the need for closer scrutiny of the mechanisms underlying the nervous system's vulnerability to chemical substances, as well as the need for improved premarket testing and hazard communication. Our goal for the 21st century could be to prevent the long-term neurotoxic effects of chemicals by predicting their effects from their structure and preventing or limiting human contact. A vast chasm of biomedical ignorance must be filled through research advances if this goal is to be achieved.

Redirection of funds used for one fighter plane will more than double the total Federal budget now devoted to neurotoxicology research.

Thank you, Senator.

Senator REID. Would you read that last sentence again? What did you say?

Senator WARNER. I can repeat it. [Laughter.]

Senator WARNER. Removal of one fighter plane will allow enough funds to come into the budget. Am I not correct?

Mr. SPENCER. That is correct, Senator.

Senator WARNER. Of course he didn't identify whether it was a B–2 or—[Laughter.]

Senator REID. Doctor Schaefer.

STATEMENT OF MARK SCHAEFER, STUDY AND PROJECT DIRECTOR, OFFICE OF TECHNOLOGY ASSESSMENT, ACCOMPANIED BY ROGER HERDMAN, ASSISTANT DIRECTOR FOR HEALTH AND LIFE SCIENCES, OTA

Mr. SCHAEFER. Thank you, Mr. Chairman. I will summarize my written testimony.

I was formerly a Project Director at the Office of Technology Assessment. With me is Doctor Roger Herdman, Assistant Director of OTA for Health and Life Sciences. I appreciate being invited to testify on behalf of OTA on our recent study of Federal programs and policies directed to the neurotoxicity problem. This past spring, OTA completed its report entitled "Neurotoxicity: Identifying and Controlling Poisons of the Nervous System".

More than one out of every five Americans suffers from disorders or disabilities that involve the brain. No one knows precisely to what extent toxic substances contribute to nervous system disorders and disabilities, but they clearly play a significant role, and there is cause for concern. Lead poisoning alone is a very serious public health problem that threatens the intellectual capabilities of a large number of the Nation's children. The ongoing efforts of your Committee and others to address the lead poisoning problem illustrates how difficult it can be to control a dangerous neurotoxic substance once it has been widely used in commerce.

Neurotoxic chemicals are chemicals that adversely affect the structure or function of the nervous system. The nervous system includes the brain, the spinal cord, and the vast array of nerves and sensory organs that control major body functions.

Every organ system may be adversely affected by toxic substances, but the nervous system is particularly vulnerable. Furthermore, the nervous systems of the fetus, the child, the elderly, and workers in certain occupations are particularly susceptible to these substances.

First, I would like to describe the nature of the neurotoxicity problem and the scope of Federal research and regulatory programs directed to it. Then I will outline some of the findings of our study and possible policy approaches to improving the Federal response to this important public health problem.

The brain, spinal cord, and nerves throughout the body depend on a delicate balance of chemicals for proper functioning. There are many opportunities for foreign chemicals to disrupt this balance. The first figure on your right illustrates the fundamental structure of the nerve cell and summarizes the reasons why the nervous system is vulnerable to toxic substances.

Neurotoxic substances may block the channels through which charged molecules flow and thereby inhibit electrical signalling between cells. Toxic chemicals may disrupt the synthesis or degradation of neurotransmitters, the chemical messengers that travel between nerve cells. They may block receptors, the sites at which neurotransmitters attach in a lock and key fashion, to effect chemical changes in other nerve cells. Toxic chemicals may also disrupt the activity of the enzymes that catalyze the biochemical reactions that take place within nerve cells.

If the damage caused by a foreign chemical is severe enough to kill a nerve cell, the damage is likely to be permanent, because unlike many other cells of the human body, nerve cells normally do not regenerate.

As indicated in table one, neurotoxic substances can cause a variety of adverse health effects, ranging from impairment of muscular movement to disruption of vision and hearing, to memory loss and hallucinations. This particular table divides the effects into five major categories: motor effects, mood and personality effects, sensory effects, cognitive, and general effects.

Some substances can cause paralysis and death. Often, neurotoxic effects are reversible, that is, the effects diminish with time after exposure ceases and no adverse effects may remain. However, in other instances the effects may be irreversible and lead to permanent changes in the nervous system.

The next figure shows normal nerve fibers in a region of the monkey brain that produce the neurotransmitter serotonin. The figure on the left is a control and shows what you would normally see. The figure on the right shows the brain of a monkey that has been exposed to the abused drug MDMA. You can see that the number of fibers is decreased significantly. As this example illustrates, toxic substances have the ability to selectively kill certain subsets of nerve cells in specific regions of the brain. This specificity is a matter of great concern to neurotoxicologists.

The possibility that toxic substances contribute to the cause of some neurological disorders is often referred to as the environmental hypothesis. This hypothesis has received increasing attention in recent years, in part because of new discoveries of toxic chemicals that cause disorders with symptoms that are similar to those of known neurological disorders.

Toxic substances clearly contribute to some neurological disorders, but at this point, the extent and nature of their contribution is unclear. As Doctor Spencer pointed out, much more research is needed to unravel the relative contributions of genetic and environmental factors to diseases of the nervous system.

Just last year, a neuroepidemiological study provided evidence that the incidence of two neurological disorders may be increasing in the elderly. The top graph in the next figure suggests an increase in the incidence of Parkinson's Disease in the elderly over the period from the early 1960s to the early 1980s. The lower graph provides evidence of an increase in motor neuron disease—most often diagnosed as ALS, or Lou Gehrig's disease—in the elderly over the same period. Exposure to toxic chemicals may be one of the factors contributing to this increase. More research is neces-

sary to confirm this trend and to determine the underlying causative factors.

There are already more than 65,000 chemicals in the EPA's inventory of toxic substances, and as you pointed out, each year the agency receives some 1,500 notices of intent to manufacture new substances. Although many of these chemicals are probably harmless at low levels of exposure, some are not, and the health threats that they pose should be taken seriously.

The difficulty we face, as you pointed out, is that few chemicals in commerce have undergone sufficient toxicological testing. Therefore, we have an incomplete understanding of the risk they pose to humans and the environment. Experience tells us that every time we introduce a new chemical into commerce that has not been adequately tested, we spin the roulette wheel and gamble with the public health.

OTA's report describes the state of the present Federal regulatory and research system with respect to neurotoxicity. In the course of our study, we found that Federal research and testing programs are of insufficient size and scope to address the problems created by these substances. Research programs with respect to environmental neurotoxicology are small and receive relatively little Federal support given the possible magnitude of the problem.

Most of the Federal research effort in environmental neurotoxicology is confined to the intramural research program at EPA and the extramural grants program sponsored by the National Institute of Environmental Health Sciences.

In addition, the National Institute for Occupational Safety and Health has very little money to support neurotoxicology research, even though it is the principal Federal agency responsible for research on chemicals found in the work place. Some years ago, NIOSH identified neurotoxic disorders as one of the Nation's ten leading causes of work-related disease and injury, yet the agency lacks funds to conduct a research program to understand the problem.

Federal regulatory agencies are just beginning to take steps to identify and control these substances. The EPA has developed neurotoxicology test guidelines that can be used in regulatory programs. However, these tests will have to be required more frequently. In addition, more advanced tests must be developed to complement those that are already available. In vitro neurotoxicity tests, for example, may be useful in screening chemicals to help determine which substances should be subjected to more comprehensive testing.

I'll just very briefly mention the problem associated with the Toxic Substances Control Act. TSCA requires manufacturers to notify EPA in advance of the intended introduction into commerce of a new chemical through pre-manufacturing notices. The act does not require that manufacturers carry out any specific program of toxicity testing. However, if toxicity testing has been undertaken voluntarily in advance of submission of the PMN, the manufacturer must submit the data to EPA.

So this requirement may act as a disincentive to testing, in that manufacturers recognize that if they conduct tests and submit the data to EPA as part of the PMN, the information could lead the

agency to conclude that the chemical presents an unreasonable risk. Therefore, the law as written presents an incentive not to undertake toxicological tests prior to submission of the PMN.

I'll only briefly summarize some of the steps Congress could take if it wished to take further action to address the neurotoxicity problem. From the regulatory standpoint, numerous laws either directly or indirectly control these substances. Congress could mandate more extensive neurotoxicity testing under TSCA and FIFRA; mandate that neurotoxicity concerns be given greater attention when making regulatory decisions with respect to toxic substances; and it could enhance Federal laws focusing specifically on exposure of children to lead.

With respect to Federal research efforts, Congress could take steps to enhance neurotoxicology programs at or sponsored by various Federal agencies. Congress could also promote more effective coordination of Federal research and regulatory programs.

With respect to the research and health care personnel issue, Congress could take action to enhance pre- and post-doctoral research training programs in neurotoxicology by providing funds to support more training grants to individuals and/or research centers.

Finally, assuring that the public is adequately informed of the risks that toxic substances pose is of major importance. Congress could take steps to ensure that workers—particularly women of child-bearing age—receive sufficient information on the neurotoxic potential of chemicals, both at home and in the work environment.

In addition, Congress could require that neurotoxicity concerns be explicitly described in information developed and released under the Federal Emergency Planning and Community Right-to-Know Act, and it could mandate improved labeling of consumer products with respect to potential neurotoxic effects.

Mr. Chairman, thank you again for inviting OTA to testify today on this important issue. We would be happy to assist the Committee in the future as your work in this area progresses.

Senator REID. Thank you, Doctor Schaefer.

We have been joined by Senator Jeffords, a member of this Subcommittee and a member of the full Committee.

Senator Jeffords, do you have a statement?

OPENING STATEMENT OF HON. JAMES M. JEFFORDS, U.S. SENATOR FROM THE STATE OF VERMONT

Senator JEFFORDS. Yes, I do, Mr. Chairman, but I would be happy to submit that for the record. I do have some questions also that I would like to have the opportunity to ask, as time permits.

OPENING STATEMENT OF HON. JAMES M. JEFFORDS, U.S. SENATOR FROM THE STATE OF VERMONT

I want to thank the Office of Technology Assessment for conducting this study. I noticed in reading this document that there is a significant amount of information on the effects of lead exposure—an area of interest to many of us on the Committee thanks to the efforts of Sen. Reid.

In the past decade, there have been several incidents in Vermont where workers and their families were exposed to neurotoxic agents, in particular, lead and mercury. I also noticed that pesticide exposure is discussed in this report. As Vermont is

an agricultural state, the potential exposure of my constituents to pesticides is also an important concern to me.

I am glad that we are continuing to realize that there are other than carcinogenic risks associated with chemicals. For example, as we meet here, EPA Region IV and the Agency for Toxic Substances and Disease Registry are responding to an incident in North Carolina where workers at an incinerator have potentially suffered neurological effects. These workers apparently were not provided adequate protective equipment or training, and their health has suffered as a result.

In setting our national policies, however, we must be careful to consider all risks to our citizens, not just those posed by neurotoxic agents. Sometimes we seem to rush to keep our laws abreast of the new scientific discovers, while forgetting the risks we learned of years, months, or even days before.

For example, EPA has issued regulations controlling the application of sewage sludges to farm land. EPA estimates that these regulations will prevent 21 noncancer health effects, such as hypertension, and 0.06 cancer cases at a cost of over $15 million. This cost averages out to $722,000 per health effect prevented.

As a nation, I wonder if we can continue to afford this cost. For $722,000, I believe we could provide adequate prenatal care to more than 21 expectant mothers, or we could provide food and shelter for homeless families. We could even provide health insurance for hundreds of people so that they could get quality medical care.

I would thus ask the witnesses in their responses here today and in their future efforts to consider how we reduce the costs of protecting the public from neurotoxics. Is it better to control the production or the distribution or the use of a product when setting guidelines? For example, my colleague, Sen. Reid, has proposed limitations on the use of lead in products. Others propose limitations on disposal. It seems that it would be cheaper to prevent the manufacture of a potentially harmful product than to control its ultimate disposal. The witnesses thoughts on and consideration of this issue today and in the months ahead would be appreciated.

Thank you Mr. Chairman.

Senator REID. Okay.

Could both of you gentlemen give us your professional background and experience, including education.

Doctor Spencer.

Mr. SPENCER. Senator, I was trained at the University of London, received my Ph.D.—actually from the Faculty of Medicine, which is a slightly unusual thing from the American standpoint. I came to the United States in 1971, took citizenship and became Professor of Neuroscience, Neurology and Pathology at the Albert Einstein College of Medicine in New York. So my background is both in neuroscience and neurotoxicology.

Two years ago, I left to set up a Center for Research on Occupational and Environmental Toxicology at the Oregon Health Sciences University in Portland, I think probably the first one in the country devoted almost exclusively to neurotoxicology.

Mr. SCHAEFER. Mr. Chairman, I received my undergraduate degree at the University of Washington, and my Ph.D. at Stanford University in the neurosciences. My graduate work was supported by a fellowship from the National Institute of Mental Health. Afterwards, I was a congressional fellow at the Office of Technology Assessment. And in between my undergraduate and graduate work I worked for EPA for about five and a half years.

Senator REID. Thank you very much.

Doctor Spencer, I was stricken by a statement that you made in your testimony about the long-term cost if Parkinson's Disease or Alzheimer's Disease could be controlled. It certainly would be significant. I remember that I had occasion to have dinner with the President of the National Alzheimer's Foundation. This was a number of years ago. He made the statement that unless we did something to bring Alzheimers under control, it was going to basi-

cally break the Medicare Program. Well, the Medicare Program hasn't become any healthier since then. I don't know if he really knows the overall costs of the Medicare Program, but it is a significant factor in the ongoing health care costs of this Country.

What you're telling us is that Parkinson's Disease—which by the charts is certainly becoming more predominant—Alzheimer's Disease, and Lou Gehrig's Disease—what you're telling us is that these may be caused by chemicals in the atmosphere, things that we're using in the work place, et cetera. Is that right?

Mr. SPENCER. Yes, Senator. I suppose the dramatic improvement in health standards in developed countries has resulted in very good news for humans resident therein, namely that we'll all live much longer than we ever anticipated. The bad news is that we will not remember why we wanted to live longer. [Laughter.]

Mr. SPENCER. The reason for this is that the brain is provided with a certain group of cells, certain subsets of cells, which over the course of time, as a natural consequence of the aging process, is paired down. If one intervenes at some point, at any point during life, with a chemical substance which is also able to affect the very same population subject to age-related attrition, then one is able to bring forward the inevitable consequence of the cluneal appearance of this nerve cell deficit.

I should say, as a note of caution, that we do not have any solid evidence that chemicals within the occupational and general environment do trigger any of the three diseases that you mentioned. However, because of some very active research supported initially by the National Institutes of Health, and subsequently conducted extramurally, of the remarkable condition that occurs in three spots in the Western Pacific region, including Guam—we know that, as a result of that research, as yet unidentified chemical factors trigger a disease which resembles, to a remarkable degree, a mixture of Lou Gehrig's Disease, parkinsonism, and a form of progressive and fatal dementia.

What is so remarkable about that particular disorder is that it has changed its face over a period of time. In the 1940s, 1945, the disease looked more like Lou Gehrig's Disease, and today it looks like Alzheimer's Disease—from this evidence, and secondly from the evidence of heroine addicts who were exposed to a street drug containing the compound MPTP, a compound which is now proven to be the cause of parkinsonism—almost identical to Parkinson's Disease in human subjects, we know that these late-life—or what are normally considered to be late-life—degenerative diseases can be triggered by chemical substances.

So there is a tremendous need for research to find out what role chemical substances have in triggering Alzheimer's Disease, Parkinson's Disease, and Lou Gehrig's Disease. The problem is that we know from the Guam experience that the latency may be up to 35 years between exposure to the environmental substance and the appearance of the disease. That means that certain U.S. military and civilians who were in Guam and exposed to that environment may be today expressing the adverse health consequences of living in that region.

Senator REID. What is this substance that you're not telling us about?

Mr. SPENCER. I'm being cautious because science dictates that. The major suspect agent in that particular setting is a highly toxic plant that is used as a food or medicine in all three high-incidence foci of disease.

From that work, we are searching for the precise chemical structure so that we can now look for the chemical elsewhere in the environment. It doesn't mean to say that it's going to turn up in a plant. It could turn up in a variety of different foci.

But the big news is that environmental factors clearly trigger this fatal disease. That represents a revolution in thinking about the problem of neurotoxicity.

In contrast to what Doctor Schaefer emphasized about the reversibility and the irreversibility of such effects, this puts us in a totally different environment in which we're talking about not only irreversible but also progressive and fatal effects. It puts us in the same league as cancer.

Senator REID. Doctor Schaefer, for the benefit for those of us who are not doctors or scientists—which I think includes a lot of people in this room—what distinguishes neurotoxicology from traditional toxicology.

Mr. SCHAEFER. I think it's primarily that we're focusing on a specific organ system that is unusually vulnerable to toxic substances. And, as I pointed out in my testimony, the nervous system depends on very delicate balances of chemicals. While there are a number of safeguards to detoxify chemicals, the system can be overwhelmed. And you can see a whole range of problems. I think that, particularly with respect to children, the fetus, the developing nervous system, you have to be extremely careful because this is a time when the system is actively being wired, billions of nerve cells are making connections with each other——

Senator REID. As we learned in lead poisoning.

Mr. SCHAEFER. That's right. And the Minamata Bay incident in Japan with mercury poisoning—rather serious disorders can result.

Senator REID. Doctor Spencer, in the second page of your testimony you said something that certainly got my attention. "Substances approved for use as food additives, health foods, fragrance raw materials, and", the one that got my attention—I hate to bring out all the dirty linen in the hearing—but "anti-dandruff shampoos"—what do you know about anti-dandruff shampoos?

Mr. SPENCER. One of the leading anti-dandruff shampoos has an anti-seborrhoeic agent, anti-dandruff agent, which when reportedly spread on the unbroken skin of animals (rats) results in paralysis. Of course, this does not necessarily mean that it will result in damage to humans.

Senator REID. I think I'm going to go for a little flaking from now on. [Laughter.]

Mr. SPENCER. This does not mean necessarily that it will elicit neurological disease in humans. But no one has ever really investigated this problem. But it's there, and it's an over-the-counter preparation.

Senator REID. Do they all have it?

Mr. SPENCER. No. Certain hair coloring agents contain lead. In addition, I have discovered through my own research, two chemicals which were widely used as fragrance raw materials in sham-

poos, soaps, underarm deodorants, and perfumes which when spread repeatedly on the unbroken skin of a rodent results in brain degeneration which is irreversible, as well as changes in the spinal cord and penophenal nerves.

Mr. SCHAEFER. Mr. Chairman, could I briefly follow up on that?

Senator REID. I'm going to stop using deodorant, too. [Laughter.]

Mr. SCHAEFER. I just wanted to mention that when we deal with carcinogens we tend to think in terms of "no threshold", that is, that if we're exposed to the substance there's a chance of developing cancer. With non-cancer health risks, we tend to think in terms of thresholds. So something may have neurotoxic potential, but unless you're exposed to a certain level dosage of the substance, then there may not be a problem. It's useful to keep that in mind when talking about substances that have the potential.

Mr. SPENCER. May I interject something? Because the nervous system has so much functional reserve, at my age the subtle effects of damage from such an agent may not appear immediately.

Senator REID. You're real pleasant. [Laughter.]

Mr. SPENCER. But if I'm fortunate to live to a ripe old age they may well appear at that time.

Senator REID. That's one of the questions that I have.

Your testimony does discuss the latency period that occurs from the time someone is exposed to a neurotoxin until the disease manifests itself. You say it could be decades later. Do we now have any accepted tests to screen these chemicals for latent toxic effects?

Mr. SPENCER. No, we don't.

Senator REID. That's what you're working on, I assume.

Mr. SPENCER. Yes. A lot of people are now working on this. In fact, I've just broken away from a conference in Arkansas that was dealing with this very issue today and tomorrow. We are hunting for the chemical structures which have the potential to cause this type of effect. We do know it's very likely that it will be those chemical agents which hit parts of the brain that normally decline in structure of function as a consequence of age. Any chemicals which are going to be targeted against those areas are likely to cause these long latency effects.

Senator, 20, 30, or 40 years ago we would have laughed at anyone who suggested that cigarette smoking could cause lung cancer 30 years later. We now accept that as a fact of life. We are, in 1990, with respect to certain neurodegenerative diseases, at about the same stage that we were 30 years ago with respect to cancer. We're in a situation where we're just waking up to the fact that certain types of chemical substances are able to target those areas of the brain which are susceptible to aging. And we are realizing now that latent health effects, spanning up to half a century, may result from exposure to certain chemical substances.

That certainly doesn't mean all of them. We need to find out which ones are the problems.

Senator REID. Let me advise the panelists and also the Committee. The staff advised the panelists that they would have eight minutes to present their testimony, which we have fixed the timer to that. Also, what the panel members are going to do is also be bound by the same eight minutes. If we need more time, we'll go another round.

Senator Lieberman.

Senator LIEBERMAN. Thank you, Mr. Chairman.

Doctor Spencer, just to pick up on a few things that you just said, do I understand correctly that the typical progression here is that these neurotoxins accumulate within the system? In other words, an older person might be affected not just because his own defenses might be down but because the neurotoxins have accumulated to a point where they are more powerful?

Mr. SPENCER. Senator, there are two possible effects. One you have identified, namely that the chemical will accumulate in some store within the body. Indeed this is recognized with certain metals, such as lead. But, in fact, more commonly it is the notion that exposure to a chemical may produce effects that accumulates. The chemical may disappear, but the effect can accumulate with time.

And the third possibility, which is under active consideration at the present time, is that there may be a class of chemicals which is able to interact with nerve cells and irreversibly set them on a declining course toward cell death. That's the most speculative, the latter.

Senator LIEBERMAN. Just to follow up on a personal question, if I may, are you worried enough about the potential neurotoxic effects of some of the consumer products that you have described to stop using them now, or do we just have warning signs?

Mr. SPENCER. I would say that in relationship to certain chemicals that may be found in health food stores, fragrance raw materials, and certain shampoos, there is a need to scrutinize their ready availability as an over-the-counter product. There is, for example, no regulation for study of fragrance raw material before they're introduced into society. We actually believe, if you like, as a society that things spread on the skin do us some good, which is the most remarkably upside-down view of exactly what is happening.

We also believe, I suppose, that chemicals don't penetrate the skin because it's a perfect barrier. Nothing could be further from the truth. Certain well documented occupational neurotoxicities have in fact resulted from skin contact with the chemical substance rather than by inhalation. Acrylamide in the chemical polymer industry, methylbutylketone in the painting industry, furniture industry, et cetera, and other compounds such as the BHMH compound, Lucel 7, that Senator Reid mentioned from the Lancaster, Texas outbreak. All these penetrated skin.

Senator LIEBERMAN. Okay. So it sounds like there's something to worry about.

Mr. SPENCER. There's a lot to worry about.

Senator LIEBERMAN. Part of what you're asking for is sufficient additional research to help us make judgments about what we should do about those worries?

Mr. SPENCER. TSCA empowers the Environmental Protection Agency to look at pre-manufacture notices for the structure of the chemical and to predict whether or not it is likely to have an adverse effect. Recently, people trained in neurotoxicology have been part of that process.

This, I think, is an excellent way to proceed in the year 2050, but in the year 1990 we have next to no knowledge about the relation-

ship between chemical structure and toxic effect. What we need is a large amount of research to try to draw the base of knowledge forward from simply counting the number of people that are paralyzed and searching for the chemical that caused it, and to find out what particular types of chemicals are likely to cause paralysis and prevent them from getting into commerce.

So while the notion of reviewing the structure and predicting the activity is, I think, an excellent ultimate goal, and one that EPA is pursuing at the present time, they have almost no information to go on because the scientific base is not there. That's where the research dollars are needed. That would involve greater research in animal studies, in tissue culture studies, and in structure-activity studies.

Senator LIEBERMAN. You've actually anticipated my next question. Obviously we're dealing here, as we all know too well, with limited resources. A question in an area of this kind is, what are the priorities? I think you've given a pretty good statement, but do you want to refine it any further? If we were to apply additional resources to this area, particularly in research and testing, what should the priority allocations be?

Mr. SPENCER. I would say that 20 or 30 years ago we had a suspicion that certain chemicals were able to cause cancer. We declared a war on cancer. We created a National Cancer Institute. We created a vast amount of biomedical research focused on this issue. Why? Because this is a long-latency terminal condition.

We now understand that, in relationship to neurotoxicity, we are also dealing with long-latency terminal conditions, not ones that kill you quickly, ones that may chronically impair the individual and produce a great burden for society not only for families but also for the nation's purse.

So investing in America's future by investing in research that will lead to the prevention of disorders will save us a vast amount of money in treating those disorders once they appear.

Senator LIEBERMAN. I think that's a good point. One of the things that we found with lead poisoning—and it's true with a lot of the neurotoxic effects and perhaps all—is that for a long period they are invisible—at least as we understand that term—therefore it's harder to engender concern and then action to do something about it.

Let me ask an awkward question—and we shouldn't have to ask these questions. I acknowledge that your field is neurotoxicity, so one might say you're biased. Are we allocating too much to the research and testing in the area of carcinogenic effects? Should we be, in a limited resource climate, redirecting some of those to neurotoxic research and testing?

Mr. SPENCER. Frankly, I don't think that I'm in a position to be presumptuous enough to talk about redirecting funds from one area of research to a second. But I would say that certainly the area of neurotoxicity is an area that is going to prove to be at least as important as our current focus on chemically induced carcinogens.

Senator LIEBERMAN. Thank you. I appreciate that answer.

Doctor Schaefer, let me just quote—Dr. Spencer touched on this—from the OTA report that—

Thousands of new industrial and consumer chemicals manufactured each year are typically subjected to far less toxicity testing and evaluation under TSCA than the smaller number of new pesticides, food additives, and pharmaceutical chemicals registered under other Federal laws.

My question is, should we be doing more testing under TSCA? Should all chemicals be tested, or do we need to establish some criteria to determine which should be tested?

Mr. SCHAEFER. I think we definitely should be doing more testing under TSCA, particularly with respect to the new chemicals that are coming into commerce and the existing chemicals that are produced in fairly large quantities. I think it's unrealistic to say that we should be doing neurotoxicity testing across the board for all the chemicals in commerce. I think, just given the economics alone, that option is probably impractical. But, you're right. We do have to find some mechanism to set priorities. EPA has ways of doing that.

The difficulty in recent years is that not that many chemicals have been tested, in general, and very, very few have been tested with regard to neurotoxicity specifically. That's a weakness of TSCA and a weakness of our regulatory programs right now.

Senator LIEBERMAN. Thank you.

Senator REID. Senator Jeffords.

Senator JEFFORDS. Thank you, Mr. Chairman.

Doctor Schaefer, I'll be picking on you and give Doctor Spencer a rest here a bit.

I'm the ranking member of the Subcommittee on Labor, thus I have been concerned or intrigued by the difference in standards which we use in some of our work situations versus what we use generally in the Clean Air Act. For instance, we were talking about the risk 10 to the minus fifth, minus sixth in the work place. We're talking about risk 10 to the minus third and things like that. So I have some questions about coordination and understanding between the various agencies, whether these things come about basically because of the assumption of the risk type thing, a lack of understanding, or what.

In your report, there is some discussion about the coordination between various Government agencies and their regulations about neurotoxicity. How well, in your opinion, do NIOSH and OSHA coordinate their activities with other Government agencies and between themselves? What improvements could be made to better the relationship between these agencies?

Mr. SCHAEFER. With regard to interactions between NIOSH and OSHA, I think there's a consensus that there is a major weakness there. There's a lot of reasons for that. NIOSH does not seem to have the total confidence of OSHA, for whatever reason, and OSHA has often looked to other organizations, such as ACGIH, in developing standards.

I think that part of the problem is that you have OSHA and you have NIOSH. They are separate agencies. There's really no one above them saying, "Look, fellows, you have to work together, you have to plan things better, and you have to develop regulatory strategies together."

Now, as far as the relationship between OSHA and NIOSH and other Federal agencies, I think I'd just as soon make a general

statement there that cooperation and coordination between Federal agencies could be greatly improved. OTA held a workshop on this subject, specifically, and brought in agency managers, regulatory officials, and research officials and discussed for some time the various approaches that they could use to coordinate things better. They're now—at least in the neurotoxicity area is an interagency committee on neurotoxicology, and perhaps Doctor Reiter, when he testifies, could say something more about that.

Senator JEFFORDS. I thank you also in respect to EPA and OSHA.

In the work place, as I mentioned, we sometimes have different standards. Whether that's good or bad or whatever is not relevant to my question. Have you noticed any differences in the protection with respect to the different standards to protect families so that when someone comes from the work place they don't carry with them the types of toxicities that they're exposed to in the work place on their clothing? Are there sufficient standards in OSHA to guard against bringing these toxicities out the plant gate?

Mr. SCHAEFER. We didn't look specifically at the contribution that clothing and these secondary transfers make to exposure, although it's well-recognized that there is a problem there, particularly with pesticides, for example, in agricultural work.

Senator JEFFORDS. Right.

Mr. SCHAEFER. But I think your broader question—yes, there are differences between EPA, for example, and their approach to regulatory matters and OSHA. I think that there has been a difference in how vigorously these agencies pursue the mandates that the Congress has set.

There is a well-known history regarding OSHA, and I don't have to go into it. But, yes, there are very significant differences, I think, in how these agencies go about their regulatory decisionmaking. It's worthy of a closer look.

Senator JEFFORDS. Thank you very much.

Senator REID. It's the burden of the company that's placing the product into the market to show to the Food and Drug Administration that the product is safe. Wouldn't that be the best way to do it with the chemical industry, put the burden on the industry rather than have it on the Environmental Protection Agency?

Mr. SCHAEFER. That's correct. FIFRA basically operates under that general concept as well. If you're a company and you want to introduce a chemical into commerce, then it's up to you to show the regulatory agency that this product is safe and effective. Under TSCA, you're absolutely right. There's a problem here because the burden is on the regulatory official to make a decision, but there is no mechanism to get that official the data that he needs to make an intelligent judgment about the merits of regulation.

As Doctor Spencer pointed out, if you don't give them data, then they just have to rely on structure/activity relationships. The catch 22 is that in the neurotoxicity area, we simply don't know very much about structure/activity relationships.

Senator REID. We could spend the day with you two gentlemen, but we don't have the time to do that.

Thank you very much.

Mr. SPENCER. Thank you.

Mr. SCHAEFER. Thank you.

Senator REID. The next witness today will be Ms. Linda Fisher, Assistant Administration for the Office of Pesticides and Toxic Substances from the Environmental Protection Agency.

We appreciate you being here today and would ask you to proceed with your testimony.

Ms. FISHER. Thank you, Mr. Chairman.

Senator REID. Would you also identify those that are here with you that you wish to identify?

STATEMENT OF LINDA FISHER, ASSISTANT ADMINISTRATOR, OFFICE OF PESTICIDES AND TOXIC SUBSTANCES, ENVIRONMENTAL PROTECTION AGENCY, ACCOMPANIED BY VICTOR KIMM, DEPUTY ASSISTANT ADMINISTRATOR, OFFICE OF PESTICIDES AND TOXIC SUBSTANCES, ENVIRONMENTAL PROTECTION AGENCY; AND PENELOPE A. FENNER-CRISP, DIRECTOR, HEALTH EFFECTS DIVISION, OFFICE OF PESTICIDE PROGRAMS, ENVIRONMENTAL PROTECTION AGENCY

Ms. FISHER. I appreciate the opportunity to testify before you today about EPA's program to evaluate and address neurotoxicity concerns and some of our responses to the OTA report. I am joined today on my right by Mr. Victor Kimm, Deputy Assistant Administrator in OPTS, and also by Doctor Penny Fenner-Crisp, who has guided much of our health research in both TSCA and in the pesticide program.

EPA is charged with identifying and controlling toxic chemical hazards to human health and the environment. As the OTA report suggests, EPA has long realized that risk assessment and risk management must employ strategies to address all significant health endpoints. Neurotoxicity is recognized as a critical endpoint for assessing health effects of chemicals and is used in hazard identification and risk assessment schemes throughout the agency. Numerous chemicals, such as lead and mercury, as well as many pesticides, have been regulated on the basis of concerns about neurotoxicity.

OPTS has considerable authority to gather data on neurotoxic effects through both its new and existing chemical program under TSCA, and through the pesticide registration and re-registration efforts. This information provides the basis for our risk management activities in those areas.

Let me take a moment to describe EPA's activities to assess and manage neurotoxicity risks, and lay out the challenges that we face.

In order to strengthen the database on neurotoxicity, it is necessary to have in place uniform guidelines detailing testing procedures to ensure that test data are reliable. Our ability to detect environmental neurotoxicants has improved over the years. When EPA was created, the regulatory community had few tests available to detect neurotoxicants. The Agency, in the early 1980's, developed an initial set of neurotoxicity test guidelines to be used in the implementation of TSCA.

Over the past few years, EPA scientists from our Research and Development Office, our Pesticides Office, and our Toxic Substances Office have collaborated in the revision of test guidelines.

These new guidelines will permit evaluation of key neurotoxic effects and greatly expand our ability to both detect and assess neurotoxic hazards.

EPA has been active in the international community to encourage more extensive neurotoxicity testing. In March of 1990, EPA sponsored a meeting with OECD countries to develop neurotoxicity testing. Neurotoxicity guidelines similar to the revised EPA test guidelines were proposed for adoption in the OECD countries.

EPA has been a leader in efforts to standardize the way we evaluate and interpret data in order to assess the neurotoxic potential of chemicals. The Agency is currently developing Neurotoxicity Risk Assessment Guidelines to be used across the agency in assessing these risks. The purpose of these guidelines is to guide risk assessors, risk managers, and others in evaluating the data that we have collected.

EPA gathers neurotoxicity test data for two broad purposes: to identify hazardous chemicals and to help the scientific community focus and prioritize further research into the hazards of potential neurotoxicants.

In the first instance, data generated under the EPA test guidelines provide the basic information needed to determine if a chemical could cause neurotoxic effects. Using these data the Agency may determine if a chemical can be used without restrictions, if special safeguards are necessary, or if the chemical should be removed from the market altogether.

Section five of TSCA requires that before it begins production, a manufacturer of a new chemical must submit to EPA a premanufacture notice on PMN. If the PMN indicates that the chemical will be produced in high volume, or its uses would involve significant worker or consumer exposure, or discharge into air or water, EPA may require additional testing under TSCA section 5(e).

Chemicals not identified under one of the exposure-based criteria just discussed are also evaluated to determine whether or not their chemical structures are similar to those of other chemicals known to cause neurotoxic effects. Testing is frequently recommended on the basis of these similarities.

Under section four of TSCA, EPA can require testing of existing chemicals on the basis of either wide-scale exposure or chemical specific hazard. To date, the Agency has required neurotoxicity test data on 16 existing chemicals under TSCA section four.

In a major departure from the single chemical test rule approach, the Agency is expecting to publish, in the near future, a multi-chemical rule which proposes screening level and cognitive function tests for neurotoxicity. This will be a more streamlined approach to test rule development and is expected to obtain testing more quickly than using the traditional chemical-by-chemical approach.

In addition to collecting data through TSCA test rules, EPA receives a great deal of data under section 8(e) of TSCA. Under section 8(e), the Agency has received 164 submissions related to neurotoxicity studies. On a voluntary basis, industry has provided us with 63 additional neurotoxicity studies. Following up on this information, the Agency has required further testing of some of these chemicals.

Under FIFRA, the Agency is required to register pesticides on the basis of data adequate to demonstrate that they will not cause unreasonable adverse effects. Testing of all organophosphorus pesticides for delayed neurotoxicity has been required since the 1970s. In addition, measurement of acetylcholinesterase inhibition has also been commonly performed for the classes of pesticides known to inhibit that enzyme.

EPA is nearly ready to propose extensive revisions to the pesticide data requirements, including a proposal to require neurotoxicity screening tests for all pesticides. This proposal is consistent with the 1987 recommendations of our Scientific Advisory Panel.

The OTA report accurately describes the extent of testing that has been completed under TSCA and FIFRA, and I agree that at this point the numbers are far too small. The development and implementation of the test guidelines and test requirements have been very resource intensive activities. As our current activities show, we are vigorously pursuing testing under both of these statutes.

The Agency is currently regulating neurotoxic chemicals on a number of fronts. Under TSCA, we can limit undesirable exposure to chemical neurotoxicants by issuing significant new use regulations on existing chemicals if the Agency believes that new uses of these chemicals may pose an unreasonable risk or lead to substantially increased exposure. To date, the Agency has issued or proposed final significant new use rules on 10 chemicals based on concerns for neurotoxicity.

We also have a history of pursuing risks associated with lead exposure. It is an issue of interest to this Committee and of continued interest in the Agency.

The Agency has also banned mercury as a pesticide, except for a few remaining uses such as a preservative in some paints. This past summer, based on health concerns, the Agency got the manufacturers of mercury to voluntarily eliminate the use of mercury in indoor latex paint.

The OTA report also identified worker protection, particularly to agricultural workers. We are revising our worker protection guidelines and hope to publish them later this year, which should reduce significantly farm worker exposure to potentially neurotoxic chemicals.

As the OTA report points out, there have been extraordinary developments in the neurosciences in recent years. At EPA we have done a lot to encourage the development and implementation of testing standards and risk assessment guidelines. Tremendous effort, through our Office of Research and Development, has produced new techniques in neurotoxicity screening and assessment to aid in the identification of potential neurotoxicants. Having actively developed technical information to better understand the risks to humans from both natural and synthetic environmental neurotoxicants, we are now aggressively using our statutes to generate additional data and to control exposure to these substances.

Thank you. I'll be glad to answer any of your questions.

Senator REID. I appreciate your being here today. I understand that you had an unexpected trip to Europe. I also noticed you yawn a couple of times in the audience. [Laughter.]

I'm sure you're tired. We appreciate you being here.

The OTA report is generally critical of TSCA. This is an area that we're going to pursue further next year in this Subcommittee, but the basis for regulation in the law is defining unreasonable risk. It seems to be a basic obstacle. It would be useful if you would describe the factors that go into this unreasonable risk finding and contrast them with a standard like that used in RCRA, which is based on protection of human health and the environment.

So the question is, what exactly is unreasonable risk? You're certainly free to call upon your associates, if you desire.

Ms. FISHER. Under section six of TSCA—that's the provision giving us the authority to ban or regulate chemicals in the marketplace—the Agency has to do a weighing of the risks against the benefits of continued use of the chemical. Currently, we do an in-depth scientific evaluation of the environmental and health hazards posed by the chemical, take a look at what kind of exposures people might receive to the chemical, and weigh the uses of the chemical and the economic benefits associated with it.

We can take into account things such as quality of substitutes and availability of substitutes. We can also take into account, or look at, a graduated risk management approach so that we can look at everything from communication to complete bans of a chemical.

So we have to look at a broad spectrum of regulatory activities and balance the cost and benefits of those against the hazards.

Senator REID. This Subcommittee has had before it the ongoing controversy over alar, we've had the ongoing controversy over lead-based paints, gasoline—lead in the environment basically—and other examples that the Committee has had, other pesticides, as you're aware of, and chemicals in the work place.

The OTA report notes that Hippocrates identified that lead was toxic some 400 years before Christ. We've compiled significant evidence confirming that observation since then. Why has it taken so long for a strategy to be developed under TSCA to address lead contamination? The same with alar. I ask you the same question that I asked the other panelists. Shouldn't we shift the burden to the industry rather than leave it with EPA?

Ms. FISHER. Well, for chemicals that are on the market, that is——

Senator REID. We're stuck with those. I understand that.

Ms. FISHER. That's more difficult than new ones coming on the market. But the Agency has actually been aggressive in pursuing the reduction of lead over time. We did ban it from gasoline almost 100 percent. I think there's a little bit still——

Senator REID. But last year we had 10 billion gallons of leaded gasoline sold—10 billion, not million—in the United States.

Ms. FISHER. I believe that we have it out of all but about one or two percent of gasoline in the United States. So it has significantly come down.

Senator REID. There's no question about that.

Ms. FISHER. What I was trying to say is that we are pursuing perhaps the top exposures. Lead in gasoline was probably the most significant.

We are also looking at sources of lead exposure under the Air Act by looking at lead smelters and whether or not they are sufficiently controlled. We are looking at it in the Drinking Water Program. So from the Agency's perspective, TSCA is one tool. It is not the only tool, however. The process underway in the Agency right now is to look across our authorities and develop a comprehensive approach to reducing lead exposure. TSCA would be one of the tools that we would utilize.

Senator REID. Let's state it this way, do you feel that for new chemicals coming into the market the burden should be upon industry to show that they're safe?

Ms. FISHER. Clearly, I think the burden needs to be with industry to perform the necessary testing. We currently are looking at the statute and assessing whether or not we need to think about some changes to it. I think, in a meeting that you and I had earlier this year, we talked about an analysis that the Agency is doing of our current premanufacture program and the burdens it places on industry and the information we get, and comparing that to what goes on in Europe where they have a minimum database set required before a chemical goes into a higher level of production.

By comparing their system and ours, we want to see whether or not we might want to switch to a system that reflects a little bit more of what the Europeans are doing.

Senator REID. When will you know about that?

Ms. FISHER. We've had a little bit of trouble getting it underway because the confidentiality requirements of TSCA have made sharing of data and information with the Europeans a little bit difficult. So it has gotten off the ground later than I anticipated. It will take place throughout next year, and hopefully by the end of next year we will have that comparison.

Senator REID. You were here about a year ago and you were going, at that time, to develop guidelines and you were going to do this by going through the Science Advisory Panel review process, revised neurotoxicity testing. It's a year later now and it's my understanding, based upon what we have heard, that it's going to be awhile longer before you complete that. Is that right?

Ms. FISHER. We think the guidelines should be published in about the next 60 days.

Senator REID. Great. That's good news.

In your testimony, you stated that the EPA is close to proposing a requirement for neurotoxic screening of all pesticides. Is that right?

Ms. FISHER. That is correct. That will be part of our update of our section 158 regulations which lay out all the required testing that must be done.

Senator REID. In previous hearings, both you and Mr. Kimm talked about the schedule for reregistering pesticides. In April, Mr. Kimm indicated that of the 600 on the list, most may be completed by 1996. Is this an accurate statement?

I guess the question is, how are we progressing?

Ms. FISHER. So far so good.

Mr. KIMM. All of the initial milestones have been met. The question in that statement of mine was what "most" means.

We are on schedule. We have found, as we have gotten into the reregistration process, that a larger number of active ingredients have been dropped by registrants than the early expectations were. We are now deep into phase three, which is where they identify specific gaps and come up with programs to address those gaps and generate the new data. We are trying to build the scientific capability in house to assess that information when it becomes available.

At the moment, I think we are on schedule. I don't know whether 1996 is exactly the right time frame, but the early activity will be largely focused on the high volume pesticides to which there is significant human exposure. I think that was the context of my earlier comment which was, the major pesticides that have high exposure hopefully are at the front end of the parade and will, in fact, be assessed relatively quickly over the next number of years.

Senator REID. Senator Lieberman.

Senator LIEBERMAN. Thank you, Mr. Chairman.

Good morning, Ms. Fisher and Mr. Kimm. I was pleased to hear you indicate that you think that new test guidelines for neurotoxicity will be available within 60 days. We look forward to those.

I have just a couple of questions about them, if you can answer them. One is, generally speaking, which substances will be covered by the guidelines? Will they apply to both new and existing pesticide products, for instance?

Ms. FISHER. We will use the guidelines across the board.

Senator LIEBERMAN. You'll use them across the board. Good.

Will they cover testing for acute subchronic and chronic neurotoxic effects?

Mr. KIMM. They will deal with acute and subchronic effects. They will be selectively applied to the chronic testing. Again, we view them as a tiered approach, so you get some testing and then depending on the outcome of that, it would go much further, depending on the initial results.

Senator LIEBERMAN. Could you explain a little bit more for the record why they will only deal selectively with the chronic effects?

Mr. KIMM. Penny can answer that one.

Ms. FENNER-CRISP. That would depend in good measure on what we saw during the acute studies and the subchronic studies. There is an expectation that with subchronic exposure one could see qualitatively an appearance of effects that one might be concerned about. If you wish to pursue it further and integrate it into the chronic testing, one might not expect to see more effects, but better define the doses at which they would occur in terms of doing the subsequest risk assessment.

Senator LIEBERMAN. Okay.

Could you go into a little bit more detail, beyond those guidelines? I'm wondering whether EPA has done any work on the effect of neurotoxic pesticides on farm workers who apply them to crops. As you know, that is one of the concerns in this hearing.

Ms. FISHER. There are a couple of things. First of all, we are in the process of strengthening our farm worker protection regulations. We proposed—I believe it was in 1988 or 1989—regulations. We got over 2,000 comments on it, which was unusual. It has taken us awhile to incorporate those into a final rule.

Those regulations will strengthen things such as notice and communication to workers, protective equipment and clothing, and reentry intervals so that they will all be geared towards reducing chemical exposure to farm workers. We are concerned about these agricult rol chemicals, as well as other pesticides. They will apply across the board.

Second, we do, when we review on a chemical-by-chemical basis, take into account farm worker exposure. We do not look only at dietary risk when we review old pesticides as well as new pesticides.

Senator LIEBERMAN. Does that include potential reproductive effects of the exposure on farm workers?

Ms. FISHER. We look at that when we evaluate the pesticides.

Senator LIEBERMAN. Let me ask you more generally whether you——

Ms. FISHER. In fact, I should say that we suspended a chemical before I came, when Doctor Moore was head of the office. We suspended dinoseb principally because of our concern of farm worker exposure and reproductive effects.

Senator LIEBERMAN. Would you say, generally, in this area that you feel that EPA has sufficient authority to protect farm workers and others in comparable positions from the toxic effects of pesticides?

Ms. FISHER. I think our authorities are pretty good under FIFRA. Under TSCA, we do split authority with OSHA. They are the primary regulatory body to protect workers. As we review chemicals under TSCA, we look at worker exposure and many times, because of TSCA section 9, if it is principally a worker exposure concern, we work with OSHA and to evaluate the risks the chemicals may present.

Oftentimes we find, however, that exposure to a chemical is part worker and part the rest of society. That's where TSCA might provide a better tool to regulate that chemical.

Senator Jeffords wondered about who takes into account family exposure. TSCA might be a vehicle that you could use where you not only have exposure in the work place, but exposure outside of the work place.

Senator LIEBERMAN. Let me ask you a few questions about the role of business, and your response to the Chairman's question about the burden being on business.

OTA I thought made an interesting suggestion statement when they said that they were worried that there was a disincentive for manufacturers to do voluntary testing because if they submit data that gives an indication of neurotoxicity, that can draw EPA's attention to the problem, but if they submit no neurotoxicity data, EPA might never require them to do tests. Do you think that's a problem?

Ms. FISHER. That was an interesting comment he made. You don't know what you don't know, first of all, and it's hard to make predictions.

We have found that TSCA, in one sense, might have encouraged industry to do some testing and perhaps screen out chemicals that they know will get caught up in the TSCA regulatory framework. It could also have that effect. I will tell you, though, that if they

haven't done the right kind of testing, when we do our PMN review we can require additional testing just on the basis that we think there will be significant exposure.

So if it's a chemical that we have reason to believe is going to go into high volume production, is going to be used in a way that there will be a lot of exposure to workers, we can require, under section 5(e), additional tests. It may not be a perfect situation, but it's one way that even if they haven't done some testing, we do have some avenues.

Again, we are doing an analysis to see whether we need to improve or expand the type of database set of tests that a chemical manufacturer might need to provide before we would allow a chemical to go on the market. If we decide that's the right way to go, we would need a change in TSCA. That's why we're doing the comparative analysis now.

Senator LIEBERMAN. I hope you'll keep us informed on that.

Just following along that line, let me ask you whether you consider the cost to industry when determining what tests you require. Do you think that's an appropriate standard to apply?

Mr. KIMM. Not on testing. The testing requirements go more on a risk basis. Obviously, if there were thousands and thousands of chemicals and you sprung a test on all of them at one time, you would exceed the lab capacity to get the work done. Obviously, we're not in that kind of a problem.

Senator LIEBERMAN. Right.

So now the decision to require tests is based on the risk assessment and not on any comparative weighing of risk against cost of the testing?

Mr. KIMM. On the testing side, that's true.

Senator LIEBERMAN. But not for——

Mr. KIMM. Under section six, to regulate under TSCA, we're into the balancing or risks and benefits. There really is a fundamental difference between the pesticides program in which we have vast authority to establish up-front requirements before we license, and the TSCA program in which we are precluded from asking for specific tests on the front-end, outside of scenarios where we would have some presumption of risk.

Senator LIEBERMAN. Finally, let me ask a factual question. How many neurotoxicologists do you have at the Office of Pesticides and Toxic Substances.

Ms. FENNER-CRISP. I think only a few.

Senator LIEBERMAN. I know you never have enough of anything, but is that a serious deficiency in that particular area?

Ms. FENNER-CRISP. I would say, yes. It's hard to determine, given that there's not a job series called neurotoxicologist. They are buried in the other job series. We do have one in the Office of Toxic Substances whose primary responsibility is in neurotoxicity, and there are a number in the Office of Pesticide Programs whose own educational background and responsibilities within the office are the evaluation of neurotoxicity data, only 10 to 12.

Mr. KIMM. Since they're sitting behind me, I feel compelled to say that the few that we have care passionately about the subject. [Laughter.]

Senator LIEBERMAN. That's nice to hear. I thank you and I thank them, particularly.

Who does this work if not neurotoxicologists? It sounds to me like there's a lot that you're getting into in this area, and quite rightly so. So do you have people doing it who are not—besides these people—not well-prepared to do it?

Ms. FENNER-CRISP. Some of the primary data review might well be done by individuals who have training in more general areas of toxicology. But as you probably understand, we have a tiered review process so that not only an individual's evaluation goes forward to become part of a risk assessment or regulatory decision. There are secondary and tertiary review capabilities that are participated in heavily by those with the more significant education and the neuroscientists.

Senator LIEBERMAN. Thank you, Mr. Chairman.

[A letter from Mr. Kimm follows:]

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

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OFFICE OF
PESTICIDES AND TOXIC
SUBSTANCES

The Honorable Harry Reid
Chairman, Subcommittee on
Toxic Substances, Environmental
Oversight, Research and Development
Committee on Environment
and Public Works
United States Senate
Washington, DC 20510

Dear Senator Reid:

On October 3, 1990, your subcommittee held a hearing on issues relating to the neurotoxicity of chemical substances, where I appeared as part of a panel from the Environmental Protection Agency (EPA). In response to a question from Senator Lieberman, I made a statement regarding the role of cost in EPA's determination of testing requirements under the Toxic Substances Control Act (TSCA). I have reviewed my comments on this point, and I feel that they were generally appropriate but somewhat misleading. I am now writing to clarify the record.

As a practical matter, cost very rarely plays a part in EPA's determination of tests it will require for a given chemical, but it is not totally irrelevant to the Agency's decision. We do consider whether testing costs could adversely affect the production of a chemical. In those cases where we do find the potential for an adverse impact, we may seek to mitigate testing costs by reducing or tiering testing requirements as appropriate.

Few chemicals have benefited from such cost reduction measures. Since 1980, 106 chemicals have been subject to final test rules, and rules are "in the works" for nearly 100 more. Of these chemicals, only three have qualified for cost mitigation. In a fourth case, the affected companies withdrew from the subject chemical market after conducting the first tier of required testing, due to the cost of the second tier testing and the likelihood that the Agency would eventually regulate the chemical because of its toxicity.

Having discussed the practical significance of cost considerations in EPA's TSCA testing determinations, I would like to provide an explanation of how we approach cost in this context.

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For all Section 4 test rules, OTS estimates the costs of the required testing and the potential for adverse economic impacts due to these costs. Cost estimates include both the laboratory costs of conducting the testing, and administrative costs, which are the costs incurred by the test sponsors in arranging for the testing and reporting to the EPA. To evaluate the economic impact of the testing, test costs are annualized over the life cycle of the chemical (estimated to be fifteen years) and compared with estimated annual revenues from sale of the chemical.

If test costs are found to be less than one percent of revenues, the Agency concludes that there is no potential for testing to cause adverse impact. If test costs are greater than one percent, there may be some potential for adverse economic impact. However, there are no precise measures available to indicate what percentage of revenues can be allocated to testing without adverse impact, since the market conditions are unique for each chemical.

For example, an economic analysis was recently prepared for a forthcoming proposed rule for neurotoxicity testing for ten chemicals. Test costs for each chemical were estimated to range from $484,000 to $858,000, including both laboratory costs and administrative costs. Annualized costs for each chemical were estimated at $53,000 to $94,000. For nine of the ten chemicals, these annualized costs are much less than one percent of revenue, and in most cases are less than one-tenth of one percent. In these cases, then, the testing is felt to pose no potential for adverse economic impacts. For the tenth chemical, which has a relatively low production volume, the upper bound annualized cost amounts to just slightly more than one percent of annual revenues. In the upper bound case for this chemical, then, there may be some potential for adverse economic impacts. While we are unable to gauge the actual extent of any adverse impact, we would expect it to be very limited, since the costs are so close to the one percent threshold.

Costs of proposed testing exceed the one percent threshold for about 10 - 15 percent of chemical substances. In these cases, the Agency performs a more thorough analysis of the economic impacts of the proposed testing which examines such factors as price elasticity of the affected market (i.e., whether an increase in cost for the given product will produce a corresponding drop in demand) and the cost and relative toxicity of available substitute products. This latter factor is examined to avoid creation of incentives for users to switch to substitutes which are suspected of being more toxic than those subject to the test rules.

In those cases where significant adverse economic effects are expected, or where significant price increases may encourage the

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use of more toxic alternatives, the Agency attempts, where feasible, to moderate test costs by (1) scaling back the testing requirements to those studies that are essential to risk characterization, and/or (2) establishing testing tiers under which the testing is performed over a lengthened time period. The Agency has also, on occasion, employed other methods of test cost moderation, such as encouraging processors of the subject chemicals to share in testing costs, and seeking the assistance of the National Toxicology Program in conducting the tests. Through these cost containment means, the Agency has been successful in obtaining a significant body of test data with only minor economic effects on manufacturers and importers.

I hope that this information adequately addresses the Subcommittee's questions on the role of cost in the Agency's testing program under section 4 of TSCA. Please contact me if I can be of further assistance.

Sincerely,

Victor J. Kimm
Deputy Assistant Administrator

Senator REID. Thank you very much for your testimony here today.

The final panel consists of Doctor Philip Landrigan, Chairman of the Department of Community Medicine, Mount Sinai School of Medicine; Doctor Lawrence W. Reiter, Director, Health Effects Research Laboratory, Office of Research and Development of the Environmental Protection Agency; Doctor Ronald W. Wood, on behalf of the American Psychological Association, New York University Medical Center; and Doctor Ruth Billings, Associate Professor of Surgery and Pharmacology, School of Medicine, University of Nevada at Reno.

Would the four of you come forward, please?

I don't think the three of you—there are none of you named Ruth, right?

We're missing a panelist, then. Doctor Billings, would you come forward, please?

We will start with Doctor Landrigan.

STATEMENT OF PHILIP J. LANDRIGAN, M.D., M.S.C., CHAIRMAN, DEPARTMENT OF COMMUNITY MEDICINE, MOUNT SINAI SCHOOL OF MEDICINE

Dr. LANDRIGAN. Good morning, Mr. Chairman. I am pleased to come before you today.

I'd like to begin, if I may, with your permission, by showing a short video. It's about a minute and a half long. It will make graphically the fundamental point that neurotoxicity caused by exposure to chemicals in the environment is a real entity, and potentially a devastating entity. It's a silent movie, so don't worry about the sound.

Senator REID. You thought it was silent. [Laughter.]

Dr. LANDRIGAN. It was before we got here. [Laughter.]

[Difficulties with the video.]

Senator REID. Perhaps you can tell us what we would have seen.

Dr. LANDRIGAN. What the movie would have shown you is a short clip of a previously healthy man about 30 years old who was employed, 10 years or so ago, at the Life Sciences Products plant in Hopewell, Virginia, where the pesticide kepone was produced. It was a filthy plant. When the State of Virginia became aware of the plant's existence, they shut it down within 24 to 48 hours, as well they should have.

Senator REID. Was it plastic that they were making?

Dr. LANDRIGAN. No. Kepone was a pesticide. It's a first cousin of mirex, the fire ant poison. It was sold principally overseas and in Central America for control of a boring beetle on banana crops. It was made under very unsanitary conditions. Workers were using snow shovels to shovel raw materials from bags into cement mixers where the product was made. People were eating in the production area of the factory. The factory itself was a reconverted gasoline station.

Senator REID. What did it do to this man?

Dr. LANDRIGAN. What it did to this man was to produce gross tremors so that the man was visibly shaking. He couldn't walk a

straight line. He staggered off a line that was painted on the floor. When the neurologist directed him to do the finger to nose test, a classic maneuver used to assess coordination, the man could not coordinate his motions. When the neurologist directed the man to look at a target, the man was unable to fix his gaze. Instead, his eyes were jumping about in his head. Lastly—not directly on the target here today—a number of the men in this plant had no sperm. Their ability to produce sperm was destroyed by the chemical.

I have presented this just as one very dramatic example of the numerous epidemics of chemically induced neurotoxicity that have been shown to occur in this Country and around the world over the last 30 or 40 years. Doctor Spencer mentioned a couple of them. I have listed others in my testimony.

The occurrence of these epidemics and the occurrence of isolated cases of neurotoxicity in single patients establish clearly that chemicals in the environment have the capacity to cause neurologic damage in humans. Further, these cases demonstrate that this damage can be devastating. In many cases, it is permanent.

One of the things that we have come to realize—and Doctor Spencer touched on this point—is the notion that these visible epidemics represent only the tip of the iceberg. For every visible case there is a large, still unspecified number of cases of subchronic or subclinical neurologic damage that are occurring in members of the population, that are not immediately evident in the clinical examination. Recognition of these cases requires special testing such as intelligence testing, electronic testing of coordination, and other specialized tests.

It has been shown by numerous scientists in all sectors of our society that chemicals ranging from pesticides to lead, to solvents, to certain plastic catalysts all have the capacity to cause various forms of neurotoxicity. Scientists have demonstrated further that the range of these effects is broad. They range from the loss of a few IQ points to inability to squeeze down on the urinary bladder to initiate urination in certain workers who have been exposed to plastic catalyst and have suffered paralysis of the autonomic nervous system as a result of that exposure.

One of the very fundamental questions that these observations raise—and a question that is not at all answered yet today—is the notion that perhaps some fraction of the cases that we see as parkinsonism, as Alzheimer's disease, or as amyotrophic lateral sclerosis might in fact be the end result of toxic exposures that took place 20, 30, or 40 years ago and caused only subchronic changes then. But we now hypothesize that those subchronic changes become clinically manifest as people age and as the functional reserve of their nervous system declines. This is a notion, really, that Doctor Peter Spencer has been very much in the forefront of propagating. I'm echoing here some of the thoughts that he has put forward on this issue.

None of us has any notion as to the extent of the problem of environmental neurotoxicity. We think it's there and we sense it's existence, but the magnitude is something that at the moment we can only guess at. I think there are two reasons why we are so much in the dark as to the scope of the problem. The first of these

impediments is the issue that you have been hammering at for the past 30 or 40 minutes, namely, that we have adequate test data to enable us to test for neurotoxicity on only a tiny minority of the chemicals in commerce.

The reference document here to which everyone turns on this question of testing is the report from the National Academy of Sciences, 1984, which showed that only approximately 20 percent of industrial chemicals in commerce—had adequate toxicity test data. Moreover, virtually all of those data are carcinogenic testing data. There are neurotoxic data on only a tiny fraction of chemicals.

When one asks specific questions about neurotoxic data pertaining to subsets within the population, such as the very young or the very old, we can practically count on one hand the number of chemicals that have been subjected to adequate testing there.

I was heartened this morning to learn that the Agency is making progress in neurotoxicity. I'm familiar with Dr. Larry Reiter and his work. It's good work, but at the moment it is only scratching the surface.

It's very important—I keep coming back to the medical dimension of all this—to remember that neurotoxicity is not somehow an isolated regulatory paradigm. We need instead to remember that it comes back to people and to recall that the diseases caused by exposure to toxic chemicals in the environment is for the most part not reversible. The nervous system has very little capacity to repair itself or to regenerate neurons once they have been damaged. It is fundamentally different from the liver or the skin, or the bone marrow in that respect. Therefore, the only rational approach to dealing with neurotoxic disease is through prevention. There is just no other way. Treatment is at the present time a distant hope.

There is no question at all that the best form of prevention of neurotoxic diseases is through pre-market screening of chemicals before they ever reach the marketplace. That is a position with which I think everyone in this field agrees. There is just no denying it.

There is a fundamental difference between neurotoxicity and other forms of toxicity such as cancer. Because of recent developments in therapy, we can talk rationally and with some hope about screening people for cancer and detecting it in the early stages so that we can do something about it while the precursor lesions may still be in a reversible stage.

By and large, however, that hope does not apply—at least not in the current state of our knowledge—to neurotoxicity. So we have to get in there beforehand.

Furthermore, I would emphasize strongly that it seems to me that the only prudent public policy is to presume that all chemical substances—both those already on the market, as well as new chemicals—are potential neurotoxins. In the absence of data, it is just not safe to presume that these chemical substances are safe or that they pose no hazard. We have to be very careful to distinguish between a verdict of "innocent" and a verdict of "not proven".

In my written testimony I have on the OTA report. I think overall it is a very nice piece of work. It analyzes the issues appropri-

ately, and it is properly cautious. I have significant praise for the authors of that report.

I also wanted to let you know—as I know you're already aware—that I'm chairing the National Academy of Sciences Panel on Neurotoxicity and Risk Assessment, a panel which is proceeding roughly on a parallel course, somewhat behind chronologically, the OTA report. I am precluded by the policies of the National Academy of Sciences from revealing to you prematurely the conclusions of that report. Suffice it to say, however, that we are concerned about very many of the same issues that the OTA report has touched upon, and we are proceeding along very much the same lines as the OTA. I think that it is safe to say that the conclusions of the NAS report will not be vastly different from those of the OTA report.

I would like to conclude by thanking you for having invited me here today. I would like to congratulate the OTA on a nice document. I would like also to reecho the plea that Doctor Spencer made, namely, that there is a vast need in this field of neurotoxicity for additional support for fundamental research. I hope that in the years ahead the Congress will be able to assist the Federal agencies, and particularly, the National Institutes of Health and the National Institute of Environmental Health Sciences, to move in that direction.

Thank you very much.

Senator REID. Thank you.

Doctor Reiter.

STATEMENT OF LAWRENCE W. REITER, DIRECTOR, HEALTH EFFECTS RESEARCH LABORATORY, OFFICE OF RESEARCH AND DEVELOPMENT, ENVIRONMENTAL PROTECTION AGENCY

Mr. REITER. Thank you, Mr. Chairman and Mr. Lieberman. I'm Larry Reiter, Director of the Health Effects Research Laboratory at the U.S. Environmental Protection Agency. I want to thank you for the opportunity to appear before you today and outline the goals, current scope, and future directions of EPA's Neurotoxicology Program and to briefly comment on the OTA neurotoxicology study.

I have a statement that I will submit for the record and summarize here.

Senator REID. Your statement will be made a part of the record, as will Doctor Landrigan's.

Mr. REITER. EPA is responsible for safeguarding public health from the adverse consequences of exposures to environmental agents. To accomplish this mission, EPA must be both a regulatory agency and a science agency. As a science agency, EPA carries out relevant and timely research to ensure that agency decisions are based on sound scientific information.

We share OTA's concern, and the concern of those here today, that exposure to neurotoxic agents may pose a significant health threat because a wide variety of physical and chemical agents have been demonstrated to be neurotoxic. I would point out that in an OTA report to Congress in 1984 it was estimated that approximately one fourth of the chemicals frequently encountered in industry

with toxicologic significance may be neurotoxic. However, as was pointed out by Doctor Spencer, the extent to which neurotoxic chemicals contribute to the development of neurological and psychiatric disorders remains unclear.

EPA's Neurotoxicology Program serves as the focal point for planning, conducting, and evaluating research to improve our understanding and ability to predict the effects of environmental chemicals on both the adult and the developing nervous system. This program was created in 1978 when EPA and the Food and Drug Administration signed an interagency agreement to combine two existing groups, one in EPA and one at FDA. I served as the Director of the neurotoxicology program from its inception until I became the Laboratory Director in 1988.

Today our program is one of the leading neurotoxicology programs in the world, having the ability to evaluate neurotoxicity at all levels of neurobiological organization and to study neurotoxic effects in both laboratory animals and humans. Such studies utilize methods derived from experimental psychology, neurobiology, pharmacology, biochemistry, and cellular and molecular biology.

Our research goals are to develop valid methods for detecting and quantifying neurotoxicologic effects of chemicals, to understand their mechanisms of action, and to eventually be able to predict a pollutant's neurotoxicologic properties based on an understanding of its chemical structure.

The division has approximately 70 scientists and technical support staff. In addition students and post-doctoral fellows are trained through agreements with the National Academy of Sciences and the local universities.

Our program has made significant contributions in the area of methods development and validation. It has provided methods and technical guidance to the agency for several developmental and adult neurotoxicity testing guidelines, as we heard discussed here today. Industries in the United States are beginning to routinely use these protocols, thus allowing the agency to obtain standardized data from different laboratories which greatly advances our ability to interpret the data.

A subset of these guidelines is under consideration for use by countries associated with the Organization of Economic Cooperation and Development. Research performed in our Neurotoxicology Program has also led to the development of a battery of neurological tests currently used by laboratories throughout the United States; these tests are also being standardized and validated for use internationally under the auspices of the International Programme for Chemical Safety of the World Health Organization.

Over the last decade, the Neurotoxicology Program has provided significant information on the neurotoxicity of a wide variety of chemicals including urban and indoor air pollutants, drinking water contaminants, pesticides, metals, and solvents. This research helped the agency to make regulatory decisions and provided fundamental insights into the mechanism by which these environmental pollutants adversely affect the nervous system.

Although a great deal has been accomplished in the field of neurotoxicology, much remains to be done. Numerous challenges face us and others working in the field. The inventory of chemical

agents that adversely affect the nervous system is far from complete. Data on the hundreds of known neurotoxicants in the environment need to be developed in order to identify and specify risk. Short term testing methods for identifying neurotoxicants, particularly in vitro methods, need to be developed and validated.

Biological markers that serve as indicators of neurotoxicant exposure and effects need to be identified. Neurotoxic risk assessments must be improved, particularly the extrapolation from high dose to low dose, from brief or intermittent to continuous exposures, and from laboratory animals to humans. These risk assessments will be markedly improved and the uncertainties will be reduced by a better understanding of the mechanisms by which chemicals damage the nervous system. And, finally, identification of the links between environmental exposure and neurodegenerative diseases, such as Parkinson's Disease, must be defined and understood.

The OTA report stresses that neurotoxicologic research should receive more attention. We agree and feel that not only EPA, but other Government agencies, academia, and industry must all be involved. We believe our program at EPA has a unique role to play. However, we do not and cannot do all that needs to be done. Interagency coordination is critical to ensuring an efficient and productive Federal research effort in this area.

For many years, we have tried to play a leadership role in this coordination. Together with OTA, we sponsored the workshop that led to the formation of the interagency Committee on Neurotoxicology. The Committee is administered through our Neurotoxicology Division and is chaired by Dr. Hugh Tilson, who directs that division.

The OTA report emphasizes the international nature of neurotoxicology issues. We fully agree and appreciate the need for international cooperation. As noted earlier, we have worked closely with OECD in the WHO's Chemical Safety Program. We also believe that carefully designed studies, particularly in Eastern Europe, may yield answers to some long standing neurotoxicity questions.

In conclusion, we agree with the OTA report that exposure to certain chemical and physical agents in the environment may pose a significant threat to human health. Many fundamental questions remain to be answered and more research needs to be done. We welcome the opportunity to work in this exciting area and to provide the scientific data needed for informed public decisions.

This concludes my statement. I will be happy to answer any questions.

Senator REID. It looks like the equipment is working now, so we'll watch the movie.

Dr. LANDRIGAN. This is a previously healthy man, roughly 30 years old who worked for approximately four weeks in a plant in Hopewell, Virginia that made kepone.

This film was kindly provided to me some years ago by the Department of Neurology at the Medical College of Virginia in Richmond.

Senator REID. He's trying to——

Dr. LANDRIGAN. He's trying to work a screwdriver there.

Now he's holding his hands out.

I am told that these deficits have persisted. They may have ameliorated slightly, but basically, they are persistent over the years since that time, which is roughly a decade ago.

Now he's doing the finger-to-nose test that I mentioned earlier, with great difficulty.

Now he's being asked to walk a straight line or to turn. You see that instead of walking with his feet close together, heel to toe, as he should have, he's walking with a broad-based gait and when he turns he has to roll himself around. He can't just do a smart about-face, not anything like a normal walk for a previously healthy man.

Senator REID. Is he trying to walk a straight line?

Dr. LANDRIGAN. Yes. They took a careful history of drug and alcohol use and other potential factors that might have accounted for this difficulty and excluded those as causes of the problem.

Here he's trying to stand on one foot. He really cannot do it.

Here's a close-up of his eyes, showing his inability to fix and focus on a target. His eyes jump about uncontrollably in his head. I think that's the end, so we can turn it off.

Senator REID. Thank you very much.

Doctor Wood.

STATEMENT OF RONALD W. WOOD, ON BEHALF OF THE AMERICAN PSYCHOLOGICAL ASSOCIATION, NEW YORK UNIVERSITY MEDICAL CENTER

Mr. WOOD. My name is Ronald Wood. I'm here representing the American Psychological Association.

Doctor Landrigan has alluded, once again, to the National Academy of Science's report in 1984. In that report, of course, the chemicals in commerce—which represent about 45,000 chemicals, as I recall—80 percent of those chemicals have no toxicity information available about them at all. I'd like to try to address how this might have come about. How could society fail in this way?

I'd like to turn to the annual report of the President's Council of Economic Advisors of 1990. "Environmental problems arise in market economies when private individuals and businesses lack incentives to take full account of the environmental consequences of their actions. The private market does not always produce the information needed to solve public problems. Private firms typically do not realize profits from research and development aimed at understanding environmental processes or the relationship between pollution and human health. Government action is often necessary to produce such information to further public policy objectives. These market failures provide a rationale for Government action."

So there is really no incentive, under the current legislative authorities, for industry to produce such information. This is also truly not an appropriate role for universities. Universities are not there to test proprietary products. They are there to train students to perform basic research, develop methods, understand mechanisms, and so forth. Their principal role is not product safety or chemical safety evaluation.

I'm not convinced either that it's truly Government's role to test proprietary products. Many of the testing resources which are cur-

rently available are dedicated to trying to cope with the problem of cancer.

About 10 years ago, we formed a committee to follow the regulatory activities of EPA under TSCA. We were very enthusiastic that this new law might actually generate an explosion of information which would help us to understand about the neurotoxic consequences of chemicals. We've just about burned out.

I'd like to take just one example which I think is highly illustrative of our frustration in this regard, a class of chemicals called the phenylenediamines. They are present in hair dyes. They make your hair very black. In 1980, the interagency testing committee put this class of compounds on their list. There was some human evidence of a disorder associated with the use of these dyes. For example, this is a paper from January 9, 1932, the Medical Journal of Australia:

> On July 23, 1931, I saw her again in bed. She affirmed that she had spent the greater part of her time in bed since being last seen, not leaving it for two to three weeks at a time. Headaches had been and were now very severe. When the headaches were most severe, vomiting occurred, especially when the patient changed position, or sometimes even when turning in bed. Intense giddiness was present, even when the patient turned her head to the left while lying in bed. The left side of the body ached and would become numb, even including the leg. Electric symptoms were more troublesome, the patient was becoming thinner, she had no appetite and so forth (pp. 53–54). This went on for a number of months until the physician ordered her to shave her head and the symptoms resolved.

There was also some evidence from studies dating back to 1923 that if you put a few drops of these materials on the back of a rabbit it would be die in seizures in half an hour. So there was existing literature indicting this class of compounds as being very neurotoxic.

Well, two years later, EPA proposed a test rule. We commented on that at that time as well. There were two more regulatory actions that we commented on in 1986 and 1988, and the final rule was promulgated in November of 1989. It took almost a decade to produce this regulatory procedure for a chemical with gross toxicity, a chemical which may play a role in the enhanced likelihood of seizure disorders in the work place, for example.

Is this an unusual situation? I turn your attention to this GAO report, "Toxic Substances—EPA's Chemical Testing Program has made Little Progress", which appeared in April of 1990 at the request of Representative Synar.

Now under this current regulatory structure, the first step takes about a year: the ITC nominates the chemical to a list and then the Administrator has a year to respond to that nomination. About 75 percent of the chemicals that are nominated are deemed worthy of further examination. Then it goes off to the Test Rules Development Branch. According to the GAO, they average about 27 months before a test rule evolves. The testing itself may take from two to five years. So it's a very prolonged process as it is currently conducted.

Linda Fisher, in her testimony before Representative Synar's Committee in July, indicated that there were about 14,000 chemicals of these 45,000 to 60,000 which were really of major concern. The Interagency Testing Committee, in 1980, identified 2,226 which might be harmful. They have managed to nominate 368 of those

2,226 in 13 years, and did 300 of those before 1980. So there is a very low rate of nomination of chemicals for further examination. Complete chemical testing data was not obtained on the vast majority of these compounds. In fact, only six chemicals had complete toxicity information as a result of this process by 1989.

Let's try to put this in some kind of quantitative perspective, to get a handle on just how fast the process is running, if it has taken them this long to get six chemicals approved. Let's assume that our public, spirited, well-motivated employees of the Environmental Protection Agency are working in the trenches every day, giving of themselves—let's say that they managed to get 20 chemicals, under the current structure, approved a year. This means that it would take about 700 years to deal with those 14,000 chemicals. If in fact they only addressed 5 percent of those chemicals, they might complete that by 2035.

The problem is severe. It's a structural problem with TSCA as a vehicle for protecting the public health. It doesn't matter how well motivated are the people who drive this truck, if the transmission is broken, you can't deliver the goods. It's my contention that TSCA is broken and needs repair.

I would turn the Committee's attention to its own report in the 98th Congress, S. 3075. In that report it says that we should change the intent of the law, that chemical manufacturers have a duty to be informed about the toxic effects of such chemicals, substances, and mixtures, and to take appropriate actions to prevent exposures that might be harmful to human health or the environment, thus, putting legal responsibility on chemical manufacturers to know about the toxicity, for their own information, so that we can be protected against dangerous health effects.

This is a major change in the climate from having this prolonged argument between the regulated industry and EPA about whether the case is adequate to start testing or not. We've made a number of other suggestions in our written testimony, which we'd like to include in the record.

Senator REID. That will be the order.

Mr. WOOD. We'd be happy to work with the Committee in any way possible to facilitate a revision of this act.

Senator REID. We have some questions we wish to ask. Senator Lieberman and I—I think I can speak for him—have had significant frustration with the things that you've just outlined. As I indicated in my earlier statement, we've had some real frustrations with alar, lawn chemicals, chemicals in the work place, dealing with composite materials, and lead. Why it has taken so long to get someplace?

Frankly, but for the action of this Subcommittee, they would still be putting alar on apples, cherries, and grapes after—how many years—14 years, 17 years, something like that. It's incredible.

Doctor Billings.

STATEMENT OF RUTH BILLINGS, ASSOCIATE PROFESSOR OF SURGERY AND PHARMACOLOGY, SCHOOL OF MEDICINE, UNIVERSITY OF NEVADA, RENO

Ms. BILLINGS. I am Ruth Billings, from the University of Nevada Medical School. I've been active in toxicology research for the last 20 years or so. What I'd like to do is to summarize the written testimony which I've submitted, and in particular to highlight some areas which have been less emphasized in other testimony today.

While we're here to consider neurotoxicity specifically, I would like to raise the question of whether it is advisable to attack specific organ systems individually, such as the nervous system, when many of the aspects of toxicity testing, risk assessment and risk management which potentially need legislative attention are applicable across the spectrum of adverse human health effects.

So throughout my testimony, while I will use examples from the neurotoxicity field, I've really approached it from the point of view of providing little distinction to neurotoxic effect and non-neurotoxic effects. But, apart from the concerns about carcinogenicity, I think we would all agree here today that there are many concerns apart from carcinogenicity that need to be addressed.

The underlying thesis of my testimony is that additional toxicity testing of substances is clearly required in order to protect our population from adverse health effects. I believe that a major area of concern is where people are chronically exposed to potentially toxic chemicals. That would, of course, be in the work place, consumer products, et cetera. The reason for this concern is that toxicity tests of these types of chemicals, particularly new chemicals, with protocols employing chronic exposure are not common.

We have very few simple tests for assessing chronic toxicity. These studies are the most costly in terms of resources. However, with our current scientific knowledge base these studies are essential when there is reason to suspect chronic toxicity. This would be particularly true with substances which are potential neurotoxins since several extremely important manifestations of neurotoxicity will only be discovered in subchronic and chronic toxicity studies. This would include behavioral effects and developmental neurotoxicity.

In my opinion, the inclusion of such tests, under specific circumstances, is more critical than requiring additional gross tests for neurotoxicity, such as the EPA's functional observational battery, since some indication of these effects would be apparent in routine toxicology tests. It is the more chronic manifestations of neurotoxicity which are totally lacking in general toxicity paradigms.

But if we are to require more testing, how can we obtain this information without jeopardizing technological advancement and with our limited resources? One way is to increase industry involvement. It has already been stated that TSCA puts the burden on EPA rather than on industry which, in my opinion, is really backward. Industry should be required to either do toxicity testing, or at the least to provide EPA with well-documented reason as to why detailed testing is not needed rather than to require EPA to come to these decisions on their own.

Another aspect of industry involvement which I think is important is to change their confidentiality provisions. This was discussed at some length in the OTA report. I think their suggestions are really adequate. I think the details of how to provide industry with essential confidentiality are very important, but I don't think that society can afford to lose so much information, which is sequestered away under the confidentiality provisions when the need for our knowledge is so great about toxic chemicals.

A second way to increase information about toxicity is to improve coordination of Federal research and regulatory programs. This has been addressed already by others. I think the best example of where improved cooperation could help the situation enormously is a closer working relationship between EPA and OSHA, the Occupational Safety and Health Administration. While they do have working relationships, it seems to people on the outside, at least in the scientific community, that there is overlap which could be improved.

I also think that how much research regulatory agencies should support in terms of intramural research and extramural research instead of relying on the links with research institutions, such as NIEHS, is something which really needs additional discussion and evaluation.

The third way to foster public health protection is to recognize the critical importance of basic research on mechanisms of toxicity and development of test methods.

I think we would all agree that there is a critical need for new, more rapid, toxicity tests, but how will new test development be accomplished, and what needs to be done to advance development at a faster pace? I think the ultimate answer lies in providing additional resources for basic research in order to improve the molecular basis of toxicity testing. The more that we understand about the nervous system, the more apparent possible rapid testing procedures will become.

As we unravel the complexities of the nervous system, we may be able to devise very simple biochemical tests for such complicated parameters as behavior, motor coordination, and learning. If we know the initiating events, such tests should be able to predict chronic toxicity as well as acute toxicity. For example, if we could identify the biochemical events which make up the learning process, we should be able to model the process and identify appropriate biochemical markers which could be measured in an in vitro test.

I believe that test development is seriously limited by our understanding, at a molecular level, of organ systems and disease processes. Increasing resources for toxicity test development is not likely to be productive unless resources for basic research are concomitantly increased. However, basic research in neuroscience will not, by itself, lead to toxicity test development. Toxicologists conducting basic research, particularly on mechanisms, are needed to bridge the gap between basic research and toxicology.

Manpower shortages in nearly all areas of toxicology are critical. The rapid decline in the availability of Federal research funds, particularly NIH funds, is having an enormous negative impact on all areas of science, including toxicology. While the actual amount of

funds appropriated for NIH has gradually increased, the percentage of approved grants that are funded has rapidly declined. A funding rate of approximately 10 percent is common among institutes for investigator-initiated individual research grants.

While it is recognized that limited financial resources creates a need for budgetary choices, it is inconsistent with our concern about toxic chemical exposure that excellent research proposals are not being funded and scientists are abandoning research careers.

Thank you, Mr. Chairman, for the opportunity to present testimony this morning.

Senator REID. Thank you very much, Doctor Billings. Your statement will be made a part of the record as will Doctor Wood's statement.

Doctor Landrigan, in your written testimony you indicate that in 1980 the cost in the United States—people diagnosed with neurological disease—is $28 billion.

Dr. LANDRIGAN. Yes, sir. We obtained those data from HCFA, the Health Care Financing Administration, in the course of the work of the NAS Committee on Neurotoxicity.

Senator REID. Ten years later, they must be even more staggering.

Dr. LANDRIGAN. It must be, given the annual increments in cost. Those just happen to be the most recent figures that we could readily obtain.

Senator REID. This figure—let's say it's conservatively $40 billion now—that's a significant amount of money each year. It would seem to me that if nothing else gets our attention, it should be just that, that the warehousing—and that's what most of the costs are—of these people is very significant. What we're talking about here today, as indicated in the film strip that you brought for the Committee, deals not with hypothetical games that scientists are playing, but real people who are affected.

I think that in our society we tend, with older people, to say, "Well, that's just part of the aging process," and just discount that, whereas some of the other dread diseases that we're spending a lot of money on, such as AIDS and cancer-related diseases, you can't attribute much of the maladies that accompany these diseases with aging. Would anybody disagree with those statements?

Dr. LANDRIGAN. I agree absolutely, and I would point out that it really wasn't much more than a generation ago that cancer was considered pretty much an inevitable concomitant of the aging process. It's only within recent memory, within the working lifetimes of the four scientists here before you, really, that we've come to pick away at the causes of cancer and realize that there are many environmental factors that are responsible for cancer.

Senator REID. Doctor, I think it's unique that you, a pediatrician, would be talking about the effects of some of these chemicals on senior citizens. Senator Lieberman—I'm sorry he's not here—has been very dogged in indicating that we need more pediatricians involved in scientific research because, even though we have concentrated today on how these chemicals build over the years, the filmstrip dealt with a 30 year old man.

The problems we've seen with lead poisoning also affect old people, but it has tremendous impact, as one of the scientists here

today indicated, when the—I forget how the term was used—but when the wires are being constructed in the human body, as they're growing. I forget what word he used, but it was very illustrative of the fact that when this growing process is taking place, chemicals can adversely affect normal growth patterns.

So I'm happy to see that you are a pediatrician and are devoting your life to these programs that are such a concern to the Committee.

Dr. LANDRIGAN. Thank you.

Senator REID. The question I have for you, Doctor Reiter, is, do you have enough help? Are you really on top of what we're trying to accomplish here? I know, you're always very hesitant to say anything, you're afraid that OMB will punish you next year, or something, but, really, do you have enough help?

Mr. REITER. Well, within the context of the overall Health Research Program in Research Triangle Park, the Neurotoxicology Program, which has approximately 24 principal investigator level scientists, is the largest single discipline outside of the cancer area. That is to say, the non-cancer disciplines, Neurotoxicology is the largest component of our Health Research Program. So we feel very strongly that, since the program was developed, it has been a very high priority research area. Obviously, we have to juggle the priorities within the confines of the budget that we have.

Senator REID. Why don't you explain to the Committee where you work and what this program is. I think everybody assumes that you're here from Washington, D.C., but you're not.

Mr. REITER. That's correct.

Within EPA the Office of Research and Development has responsibility for performing research in support of the regulatory officer of the Agency. Within EPA there is an Office of Air and Radiation, a Pesticides and Toxic Substances Office, a Water Office etc. ORD performs research in support of all these offices.

Senator REID. You're based in North Carolina. Is that right?

Mr. REITER. Within ORD, there is an office of Health Research which is located here in Washington, D.C., within that office is the Health Effects Research Laboratory which is located in North Carolina. The Health Effects Research Laboratory at Research Triangle Park has about 280 Federal employees and another 250 on-site contractors. So the laboratory is a fairly large multi-disciplinary research program in North Carolina which addresses not only neurotoxicology but also genetic and pulmonary toxicology—we are pretty much a full service bank in terms of health research.

Within that context, there is a division which focuses on neurotoxicology. It's further divided along disciplinary lines so that we are able to evaluate the nervous system at the cellular/molecular level as well as the physiological and behavioral level and to integrate that information in terms of providing better information for the agency.

Senator REID. The OTA portrays a rather dreary picture of the funding situation for neurotoxicity research in general and specifically your program. If your budget, let's say, were to double—which I wouldn't count on that—but if it were to double, what areas would you target that research, with respect to neurotoxic research?

Mr. REITER. General areas we identified in my written statement which I briefly addressed to in my testimony. These are primarily in the area of methods development. We feel that it's particularly important to begin to develop the area of in vitro neurotoxicology.

We heard today about the need to be able to test more chemicals. We heard about the complexity of the nervous system and the fact that we evaluate a variety of different neurobehavioral outcomes involving a number of systems in the brain. We feel, that in the long run, in vitro methods will be very useful for rapidly testing neurotoxic chemicals or chemical mixtures for potential neurotoxicity, and will allow us to prioritize chemicals for further testing in whole animals. It will also allow us to pursue some structure/activity relationships issues that were discussed earlier this morning.

Senator REID. Is there any money in the fiscal year 1991 request to support in vitro test development?

Mr. REITER. We have begun to do some internal shifting of resources within——

Senator REID. But the answer is, no?

Mr. REITER. The answer is no.

Senator REID. And how far away are we from having accepted and accurate in vitro methods for screening potential neurotoxic substances?

Mr. REITER. I think that goal is still quite a ways down the road. I think that there's considerable basic research.

Senator REID. Tell us what that means.

Mr. REITER. I would say that it would be six to ten years before these methodologies will become mainstream.

Mr. WOOD. Senator Reid, could I please interrupt for a moment?

Senator REID. Doctor Wood.

Mr. WOOD. Doctor Reiter, here, testifies under some restraint.

Senator REID. You don't?

Mr. WOOD. I don't. The American Psychological Association has appeared repeatedly before the HUD and independent Agencies Subcommittees of both the House and Senate Appropriations Committee, be moaning the sour state of funding for Doctor Reiter's shop. It's a very small organization, and I think his budget for neurotoxicology research this year is running about $4 million, about roughly equivalent to two program project grants in a university.

It's a small research program which has not enjoyed any growth over the past decade. It might be more revealing to ask him what, for example, the amount of money available is to an individual investigator for routine laboratory supplies.

Senator REID. That was the next question I was going to ask. [Laughter.]

Mr. REITER. The exact figure, I think, across the whole laboratory, not just the neurotoxicology program—I think when you back out salaries and expenses and other entitlements relative to the budget, it runs about $8,000/FTE, which has gone down over the last years, considering that we're basically——

Senator REID. Doctor, would you tell us what that means?

Mr. WOOD. My research program is focused on organic solvents and the use of crack. I receive $300,000 a year to do this, and we

have three Ph.D.s involved in this program. We have a supplies budget that runs about $65,000, and we think our funding is tight.

Senator REID. And it hasn't increased?

Mr. WOOD. Our funding is on a three year review cycle, and these are new awards associated with the national war on drug abuse.

Senator REID. I understand.

Mr. WOOD. But, nonetheless, in order to keep a laboratory productive and running, you have to have supplies. You have to have test tubes, paper goods, reagent chemicals, and so forth. Frequently, it would be my surmise that a laboratory investigator may find it difficult just to do his work at the bench if he hasn't behaved like a pack rat and ordered everything that he needs when he sees the money appearing shortly. There may not be enough money available to order animals, for example.

Senator REID. To order what?

Mr. WOOD. Animals, or tissue culture materials, or what have you.

Senator REID. Doctor Billings, your testimony suggests that a lot of work is needed to establish acceptable protocols for neurotoxicity. What is your view of the Environmental Protection Agency's neurotoxicity testing protocols?

Ms. BILLINGS. One of the points that I tried to make—and I'll just try to emphasize again—is that as I look at the testing protocols being discussed by EPA, they're primarily concerned with acute effects as opposed to chronic effects. So I would say that they really don't go far enough to test for possible effects that have been mostly brought out today. Neurodegenerative disease, for example, may or may not be indicated by some of these very simple tests.

Senator REID. I appreciate very much the testimony of each of you and the other panelists that were before you. We have additional questions that we're willing to submit in writing to the four of you. We would appreciate it if you responded to those at your earliest possible convenience.

The subcommittee stands adjourned.

[Whereupon, at 11:54 a.m., the subcommittee was adjourned, to reconvene at the call of the Chair.]

[Statements submitted for the record follow:]

TESTIMONY OF
MARK E. SCHAEFER, PH.D., PROJECT DIRECTOR
OFFICE OF TECHNOLOGY ASSESSMENT
U.S. CONGRESS

BEFORE THE SENATE COMMITTEE ON ENVIRONMENT AND PUBLIC WORKS
SUBCOMMITTEE ON TOXIC SUBSTANCES, ENVIRONMENTAL OVERSIGHT,
AND RESEARCH AND DEVELOPMENT

October 3, 1990

Identifying and Controlling Neurotoxic Substances

Mr. Chairman, I am Mark Schaefer, I was formerly a Project Director at the Office of Technology Assessment. With me is Dr. Roger Herdman, Assistant Director of OTA for Health and Life Sciences. I appreciate being invited to testify on behalf of OTA on our recent study of federal programs and policies directed to the neurotoxicity problem. This past Spring, OTA completed its study entitled "Neurotoxicity: Identifying and Controlling Poisons of the Nervous System." The report is the product of the collective efforts of a number of OTA staff and outside consultants who are listed at the beginning of the document, and I would like to acknowledge their excellent contributions. This report is the first of a series of OTA studies of the noncancer health risks posed by toxic chemicals. In response to your request, Mr. Chairman, OTA is currently evaluating the immunotoxicity issue and it plans to look into other noncancer health risks in the future.

As you are aware, the President designated the 1990s as the Decade of the Brain following the passage of a Joint Resolution by Congress in the Summer of 1989. The first paragraph of the

Resolution includes an ominous statistic:

> Whereas it is estimated that 50 million Americans are affected each year by disorders and disabilities that involve the brain, including the major mental illnesses; inherited and degenerative diseases; stroke; epilepsy; addictive disorders; injury resulting from prenatal events, environmental neurotoxins, and trauma; and speech language, hearing and other cognitive disorders. (Public Law 101-58)

In other words, more than one out of every five Americans suffers from disorders or disabilities that involve the brain. No one knows precisely to what extent toxic substances contribute to nervous system disorders and disabilities, but they clearly play a significant role, and there is cause for concern. Lead poisoning alone is a very serious public health problem that threatens the intellectual capabilities of a large number of the nation's children. The ongoing efforts of your committee and others to address the lead poisoning problem illustrates how difficult it can be to control a dangerous neurotoxic substance once it has been widely used in commerce.

Public concern about exposure to toxic substances tends to focus on whether or not a chemical might cause cancer. Noncancer health risks including adverse effects on organs and organ systems -- the nervous system, the kidney, the liver, the heart, the immune system -- receive comparatively little attention. Cancer is a very serious health problem, but we should not let our concern about

this disease blind us to the many other potentially serious consequences of exposure to toxic substances.

Neurotoxic substances are chemicals that adversely affect the structure or function of the nervous system. The nervous system includes the brain, the spinal cord, and the vast array of nerves and sensory organs that control major body functions. Movement, thought, vision, hearing, speech, heart function, respiration, and numerous other physiological processes are controlled by this complex network of nerve processes, transmitters, hormones, receptors, and channels.

Every organ system may be adversely affected by toxic substances, but the nervous system is particularly vulnerable. Furthermore, the nervous systems of the fetus, the child, the elderly and workers in certain occupations are particularly susceptible to these substances. First I would like to describe the nature of the neurotoxicity problem and the scope of federal research and regulatory programs directed to it; then I will outline some of the findings of our study and possible policy approaches to improving the federal response to this important public health problem.

The brain, spinal cord, and nerves throughout the body depend on a delicate balance of chemicals for proper functioning. There are many opportunities for foreign chemicals to disrupt this balance. Figure 1 illustrates the fundamental structure of the nerve cell and summarizes the reasons why the nervous system is vulnerable to toxic substances. Neurotoxic substances may block

the channels through which charged molecules flow and thereby inhibit electrical signalling between cells. Toxic chemicals may disrupt the synthesis or degradation of neurotransmitters, the chemical messengers that travel between nerve cells. They may block receptors, the sites at which neurotransmitters attach in a lock and key fashion to affect chemical changes in other nerve cells. Toxic chemicals may also disrupt the activity of the enzymes that catalyze the biochemical reactions that take place within nerve cells. And while most cells in the human body are very small, nerve cells can have long processes, providing a vast surface area for chemical attack. If the damage caused by a foreign chemical is severe enough to kill a nerve cell, the damage is likely to be permanent, because unlike many other cells of the human body, nerve cells normally do not regenerate.

At the completion of the developmental process, the brain will be made up of between 10 and 100 billion cells which will make trillions of connections with each other. How the brain correctly "wires" itself is not understood, but the chemical environment of the developing cells is certainly critical to the process. When the developing nervous system is exposed to neurotoxic substances, the process by which cells multiply and connect may be disrupted, leading, for example, to the severe retardation seen in children exposed to high levels of mercury, or perhaps to more subtle deficiencies related to learning and memory, or to neurological disorders.

As indicated in table 1, neurotoxic substances can cause a variety of adverse health effects, ranging from impairment of muscular movement to disruption of vision and hearing, to memory loss and hallucinations. Some substances can cause paralysis and death. Often, neurotoxic effects are reversible, that is, the effects diminish with time after exposure ceases and no adverse effects may remain. However, in other instances the effects may be irreversible and lead to permanent changes in the nervous system. Figure 2A shows normal nerve fibers in a region of the monkey brain that produce the neurotransmitter serotonin. Figure 2B shows the same region of the brain of a monkey that has been exposed to the abused drug MDMA. As this example illustrates, toxic substances have the ability to selectively kill certain subsets of nerve cells in specific regions of the brain. This specificity is a matter of great interest and concern to neurotoxicologists.

The possibility that toxic substances contribute to the cause of some neurological disorders is often referred to as the environmental hypothesis. This hypothesis has received increasing attention in recent years, in part because of new discoveries of toxic chemicals that cause disorders with symptoms that are similar to those of known neurological disorders. In the early 1980s, scientists discovered that MPTP, a contaminant that can be produced during the illicit synthesis of synthetic heroin, can cause the symptoms of Parkinson's disease just 5 to 15 days after exposure. And in the late 1980s, it was discovered that exposure to the toxic

substance domoic acid can cause memory loss and disorientation in matter of hours after ingestion. The cause of the disorder was traced to mussels which were contaminated with domoic acid produced by a marine alga.

Toxic substances clearly contribute to some neurological disorders, but at this point, the extent and nature of their contribution is unclear. Much more research is needed to unravel the relative contributions of genetic and environmental factors to diseases of the nervous system.

Epidemiological studies are a very useful tool in evaluating the extent and underlying causes of diseases and disorders. Just last year, a neuroepidemiological study provided evidence that the incidence of two neurological disorders may be increasing in the elderly. The top graph in figure 3 suggests an increase in the incidence of Parkinson's disease in the elderly over the period from the early 1960s to the early 1980s. The lower graph provides evidence of an increase in motor neuron disease (most often diagnosed as amyotrophic lateral sclerosis (ALS) or Lou Gehrig's disease) in the elderly over the same period. Exposure to toxic chemicals may be one of the factors contributing to this increase. More research is necessary to confirm this trend and to determine the underlying causative factors.

We are all exposed to low concentrations of many toxic chemicals in the environment, including lead, industrial chemicals, pesticides, and a broad range of other pollutants in the air we breathe, in the water we drink, and in the food we eat. In recent

decades, we have come to rely heavily on chemicals to improve our quality of life. However, our knowledge of the health risks of the substances we are exposing ourselves and our children to has not kept pace with our ambitious efforts to market new and better chemicals. There are already more than 65,000 chemicals in the U.S. Environmental Protection Agency's inventory of toxic substances, and each year the Agency receives some 1,500 notices of intent to manufacture new chemicals. Although most of these chemicals are probably harmless at low levels of exposure, some are not, and the health threats they pose should be taken seriously. The difficulty we face is that few chemicals in commerce have undergone sufficient toxicological testing. Therefore, we have an incomplete understanding of the risk they pose to humans and the environment. Experience tells us that every time we introduce a new chemical into commerce that has not been adequately tested, we spin the roulette wheel and gamble with the public health.

Two related groups of chemicals, the organophosphate and carbamate insecticides, are all neurotoxic to varying degrees. Indeed they are effective in killing insects because of their neuro-toxicological and other properties. The difficulty is that at the molecular and cellular levels, the nervous systems of insects and humans are similar in many respects; consequently, insecticides can adversely affect humans as well. The reason insecticides are normally not harmful to us is that the dose to which we are exposed is usually low. However, no one is sure what level of insecticide exposure is safe for a given individual. In

particular, little is known about exposure to low levels of multiple pesticides over long periods of time.

Metals such as lead, mercury, cadmium, and trimethyltin are neurotoxic to varying degrees and each affects the brain in different ways. Also, millions of workers are regularly exposed to organic solvents in the workplace, and many of these are neurotoxic to varying degrees.

OTA's report describes the state of the present federal regulatory and research system with respect to neurotoxicity. In the course of our study, we found that federal research and testing programs are of insufficient size and scope to address the problems created by neurotoxic substances. Research programs with respect to environmental neurotoxicology are small and receive relatively little federal support given the possible magnitude of the neurotoxicity problem. Most of the federal research effort in environmental neurotoxicology is confined to the intramural research program at the Environmental Protection Agency and the extramural grants program sponsored by the National Institute of Environmental Health Sciences (NIEHS). EPA began its intramural research program about a decade ago and it now supports more than 20 principal investigators. However, the agency has essentially no extramural grants program in this field of research to support investigators in academia and elsewhere. Typically, federal research programs involve a complementary mix of intramural research and extramural efforts. The NIEHS extramural program annually funds more than 80 grants related to the neurotoxicity of

environmental contaminants and other substances, but its intramural research effort is small. The National Institute for Occupational Safety and Health has very little money to support neurotoxicology research, even though it is the principal federal agency responsible for research on chemicals found in the workplace. Some years ago, NIOSH identified neurotoxic disorders as one of the Nation's ten leading causes of work-related disease and injury, yet the agency lacks funds to conduct a research program to understand the problem.

Federal regulatory agencies are just beginning to take steps to identify and control neurotoxic substances. The Environmental Protection Agency (EPA), for example, has developed neurotoxicology test guidelines that can be used in regulatory programs; however, these tests will have to be required more frequently if the neurotoxic potential of new and existing chemicals is to be understood. In addition, more advanced tests must be developed to complement those that are already available. In vitro neurotoxicity tests, for example, may be useful in screening chemicals to help determine which substances should be subjected to more comprehensive testing.

Some of the inherent weaknesses of major environmental laws are impeding the identification and regulation of neurotoxic substances. Let me use the Toxic Substances Control Act (TSCA) as an example. TSCA requires manufacturers to notify EPA in advance of the intended introduction into commerce of a new chemical through premanufacturing notices (PMNs). The Act does not require

that manufacturers carry out any specific program of toxicity testing. However, if toxicity testing has been undertaken voluntarily in advance of submission of the PMN, the manufacturer must submit the data to EPA. This requirement may act as a disincentive to testing, in that manufacturers recognize that if they conduct tests and submit the data to EPA as part of the PMN, the information could lead the agency to conclude that the chemical presents an unreasonable risk. Therefore, the law as written presents an incentive not to undertake toxicological tests prior to submission of the PMN.

Furthermore, because the PMN usually provides little toxicological data, EPA officials must attempt to predict the toxicity of a chemical based on its structure and what is know about the toxicological activity of similar substances. Unfortunately, in the neurotoxicological field, little is known about such structure-activity relationships; hence, it is very difficult for regulatory officials to make informed decisions about the potential health risk posed by a new chemical in the absence of adequate toxicological data.

Another aspect of TSCA that inhibits regulatory action relates to the nature of its confidentiality provisions. Nearly all of the information submitted in a PMN may be claimed by the manufacturer as confidential business information (CBI). Furthermore, under TSCA, the burden of challenging CBI claims falls on EPA; PMN submitters are not required to substantiate CBI claims unless challenged. The TSCA confidentiality provisions go beyond those

of other laws and effectively prevent public oversight of the regulatory process, add a major administrative burden to EPA, and interfere with the transfer of important information within the agency and to other regulatory agencies.

Our report discusses many other regulatory issues associated with the numerous laws that control toxic substances. Time does not permit me to discuss all of these issues this morning, but I would like to just briefly mention one of the other key findings of our study. There is a shortage of adequately trained research and health-care professionals to address the neurotoxicity problem. Improving the federal response will require funds to train more scientists to conduct research in this area, and to train physicians, nurses, and others to recognize and treat the adverse health effects caused by exposure to neurotoxic substances.

The OTA report on Neurotoxicity describes policy issues and options for congressional action in six broad categories: 1) adequacy of the Federal regulatory framework, 2) adequacy of Federal and federally sponsored research programs, 3) coordination of Federal regulatory and research programs, 4) availability of adequately trained research and health-care professionals, 5) communication of information to workers and the public, and 6) adequacy of international regulatory and research programs.

I will only summarize very briefly some of the steps Congress could take if it wished to take further action to address the neurotoxicity problem. From the regulatory standpoint, numerous laws either directly or indirectly control neurotoxic substances.

Congress could mandate more extensive neurotoxicity testing under the Toxic Substances Control Act (TSCA) or the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA); it could mandate that neurotoxicity concerns be given greater attention when making regulatory decisions with respect to toxic substances; and it could enhance federal laws focusing specifically on exposure of children to lead.

With respect to federal research efforts, Congress could take steps to enhance neurotoxicology programs at or sponsored by the Environmental Protection Agency; the National Institutes of Environmental Health Sciences, the National Institute for Occupational Safety and Health; and other agencies. Various possible actions specific to these agencies are described in our report.

Congress could also promote more effective coordination of federal research and regulatory programs. As a result of a workshop held at OTA, federal officials decided to form an Interagency Committee on Neurotoxicology to foster improved interagency coordination. Congress could formalize this Committee by, for example, providing funds to directly support its activities. In addition, Congress could mandate the submission of a report every five years on the state of Federal regulatory and research programs, including a description of research and regulatory strategies for the future.

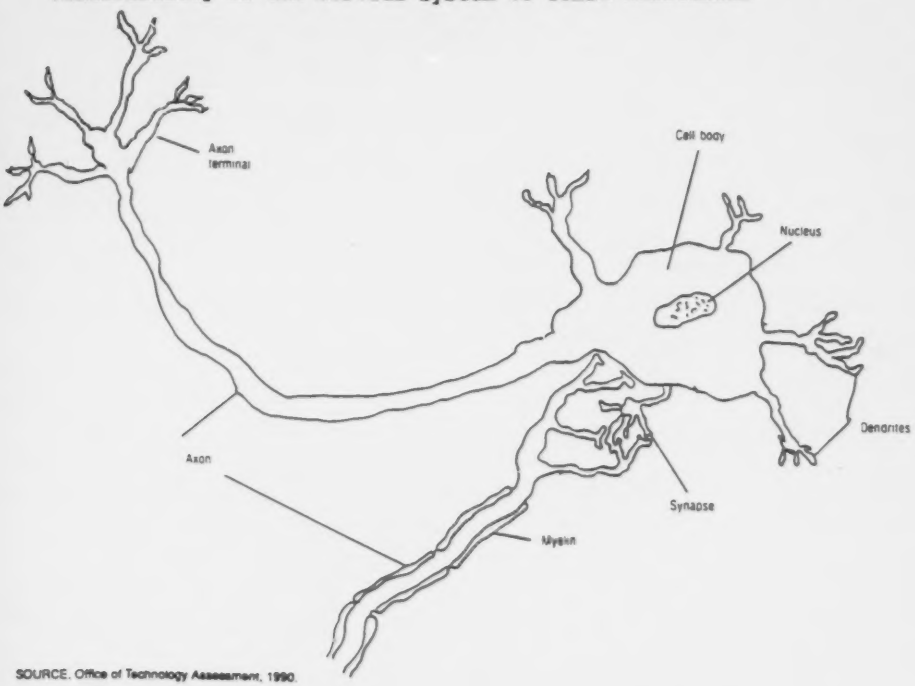
With respect to the research and health care personnel issue, Congress could take action to enhance pre- and post-doctoral

research training programs in neurotoxicology by providing funds to support more training grants to individuals and/or research centers.

Finally, assuring that the public is adequately informed of the risks that toxic substances pose is of major importance. Congress could take steps to ensure that workers, particularly women of child-bearing age, receive sufficient information on the neurotoxic potential of chemicals to which they are exposed, both at home and in the working environment. In addition, Congress could require that neurotoxicity concerns be explicitly described in information developed and released under the Federal Emergency Planning and Community Right-to-Know Act, and it could mandate improved labeling of consumer products with respect to potential neurotoxic effects.

Mr. Chairman, thank you again for inviting OTA to testify today on this important issue. We would be happy to assist the Committee in the future as your work in this area progresses.

Figure 1. The Fundamental Structure of the Nerve Cell and the Vulnerability of the Nervous System to Toxic Substances



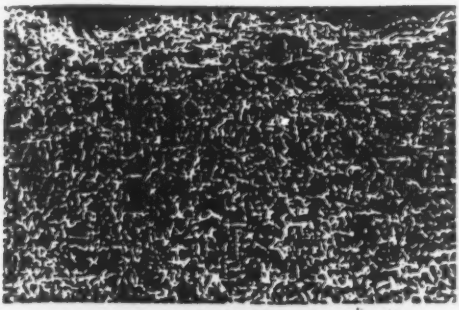
SOURCE: Office of Technology Assessment, 1990.

The nervous system is particularly vulnerable to toxic substances because:

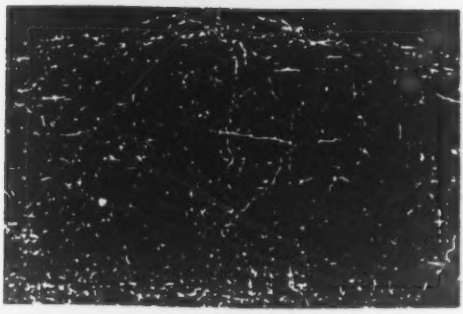
- Unlike other cells that make up the body, nerve cells, or neurons, normally cannot regenerate once lost—toxic damage to the brain or spinal cord, therefore, is usually permanent.
- Nerve cell loss and other regressive changes in the nervous system occur progressively in the second half of life—toxic damage may therefore progress with aging.
- Certain regions of the brain and nerves are directly exposed to chemicals in the blood, and many neurotoxic chemicals cross the blood-brain barrier with ease.
- The peculiar architectural features of nerve cells, with their long processes, provide a vast surface area for chemical attack and are therefore inherently susceptible to chemical interference.
- The dependence of the nervous system on a delicate electrochemical balance for proper communication of information throughout the body provides numerous opportunities for foreign chemicals to interfere with normal function.
- Even minor changes in the structure or function of the nervous system may have profound consequences for neurological, behavioral, and related body functions.

SOURCE: P.S. Spencer, personal communication, 1989.

Figure 2. Neurotoxic Effects of MDMA on Serotonin Nerve Fibers in the Brain of the Monkey



A. Control



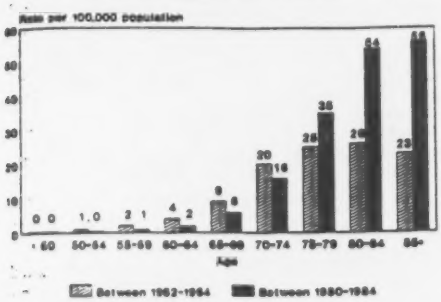
B. MDMA

Repeated administration of MDMA (5mg/kg, 8 doses) to a Cynomolgus monkey produced degeneration of most serotonin nerve fibers in this region of the cortex, which is involved in the perception of touch and position sense. Similar toxic effects are seen in most areas of the cerebral cortex.

SOURCE: M.A. Wilson and M.E. Molliver, Department of Neuroscience, Johns Hopkins University School of Medicine.

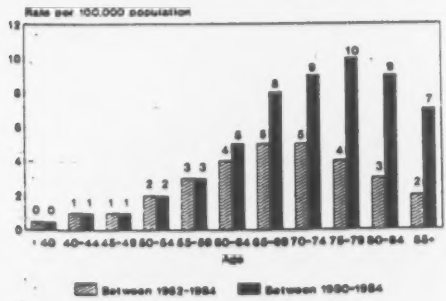
Figure 3. Average Annual Parkinson's Disease and Motor Neuron Disease Mortality in the United States

Figure 2-2—Average Annual Parkinson's Disease Mortality in the United States, White Males



SOURCE: Adapted from D.E. Lilienfeld et al., "Two Decades of Increasing Mortality From Parkinson's Disease Among United States Elderly," *Archives of Neurology*, in press.

Figure 2-3—Average Annual Motor Neuron Disease* Mortality in the United States, White Males



* Most motor neuron disease is diagnosed as amyotrophic lateral sclerosis (ALS), or Lou Gehrig's disease.

SOURCE: Adapted from D.E. Lilienfeld, et al., "Increasing Mortality From Motor neuron Disease in the United States During the Past Two Decades," *Lancet*, Apr. 1, 1989, vol. 1, pp. 710-713.

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Table 1. Neurological and Behavioral Effects of Exposure to Toxic Substances

Motor effects:	*Sensory effects:*
convulsions	equilibrium changes
weakness	vision disorders
tremor, twitching	pain disorders
lack of coordination, unsteadiness	tactile disorders
paralysis	auditory disorders
reflex abnormalities	*Cognitive effects:*
activity changes	memory problems
Mood and personality effects:	confusion
sleep disturbances	speech impairment
excitability	learning impairment
depression	*General effects:*
irritability	loss of appetite
restlessness	depression of neuronal activity
nervousness, tension	narcosis, stupor
delirium	fatigue
hallucinations	nerve damage

SOURCE: Adapted from W.K. Anger, "Workplace Exposures," *Neurobehavioral Toxicology*, Z. Annau (ed.) (Baltimore, MD: Johns Hopkins University Press, 1986), pp. 331-347.

TESTIMONY OF
LINDA J. FISHER
ASSISTANT ADMINISTRATOR
FOR PESTICIDES AND TOXIC SUBSTANCES
U.S. ENVIRONMENTAL PROTECTION AGENCY
BEFORE THE
SUBCOMMITTEE ON TOXIC SUBSTANCES, ENVIRONMENTAL
OVERSIGHT, RESEARCH AND DEVELOPMENT
OF THE
COMMITTEE ON ENVIRONMENT AND PUBLIC WORKS
UNITED STATES SENATE

OCTOBER 3, 1990

INTRODUCTION

Mr. Chairman and distinguished members of the Subcommittee, I am Linda Fisher, Assistant Administrator for the Office of Pesticides and Toxic Substances (OPTS), of the U.S. Environmental Protection Agency (EPA)and with me today is Victor Kimm, Deputy Assistant Administrator. I welcome the opportunity to speak to you about EPA's program to evaluate and address neurotoxicity concerns and our responses to the Office of Technology Assessment's (OTA) report titled "Neurotoxicity: Identifying and Controlling Poisons of the Nervous System."

EPA is charged with identifying and controlling toxic chemical hazards to human health and the environment. As the OTA report suggests, and EPA has long realized, risk assessment and risk management must employ strategies addressing all significant health endpoints including neurotoxicity. Neurotoxicity is recognized as a critical endpoint for assessing health effects of chemicals and is used in the hazard identification and risk assessment schemes throughout the Agency. The OPTS activities in this area have a strong scientific, as well as an effective regulatory component. These two components

constitute an integrated program that helps to advance the state of the science and facilitates the assessment and control of potentially neurotoxic chemicals. Numerous chemicals, like lead and mercury, and many pesticides, have been regulated based on neurotoxicity as the critical endpoint.

Neurotoxicity is defined as any adverse effect on the structure or function of the central or peripheral nervous system related to exposure to a chemical substance. Proper functioning of the nervous system is an essential element of health. Nervous system control of sensation, movement and autonomic functions is necessary for virtually all aspects of mammalian life. Because it is responsible for the integration of complex cognitive functions necessary for learning, speech and memory, the nervous system is essential for human health.

Since the nervous system is one of the most complex organ systems of the body, evaluating the neurotoxic potential of environmental agents is a particular challenge. Unlike testing for cancer, where one can look for one endpoint such as the development of tumors, testing for neurological effects requires that one examine many different effects. Testing for a toxic effect on one component of the nervous system, such as hearing, may or may not reveal a toxic effect on another component, such as vision.

OPTS has a long history of involvement in efforts to test and assess the neurotoxic potential of chemicals and control those substances possessing these properties. The OTA report

identifies EPA as the leader in developing test guidelines to evaluate neurotoxicity and suggests that regulatory programs from other agencies would benefit from joint test development. EPA has been an active participant in the recently formed Interagency Committee on Neurotoxicity (ICON). The committee serves as a forum for discussion of issues of mutual interest and a source of scientific reviewers for documents in the final stages of preparation.

EPA has also been a leader in efforts to standardize the way we evaluate and interpret data in order to assess the neurotoxic potential of chemicals. EPA is currently developing neurotoxicity risk assessment guidelines to be used across the Agency in assessing neurotoxic risks. When completed, they will describe the procedures that EPA will follow in evaluating potential neurotoxicity associated with human exposure to environmental toxicants and ensure enhanced consistency of future evaluations. They will also provide a general format for analyzing and organizing the available data for conducting risk assessments. The risk assessments prepared according to these guidelines will be used within the requirements and constraints of the applicable statutes to arrive at regulatory decisions concerning neurotoxicity risk.

OPTS has considerable ability to gather data on neurotoxic effects. Both under new and existing chemical programs under the Toxic Substances Control Act (TSCA) and through the pesticide registration and reregistration processes, neurotoxicity

information is submitted and assessed. This information provides the basis for our risk management activities in this area.

The Agency is investigating possible alternatives to limit chemical exposure on the basis of a concern about unreasonable neurotoxic effects. For example, efforts are currently underway to control the dietary risks from acetylcholinesterase inhibitors; and, certain uses of acrylamide, a potent neurotoxicant used in sewer grouting application. And, as you are well aware, another example of a neurological concern commanding serious attention both by EPA and by this committee is the potential neurological impact of lead exposure on children and their development. We are working hard to address these concerns, and commend the committee's leadership in focusing attention on this important problem.

Today I will focus primarily on the activities within OPTS to address neurological concerns. In the testimony that follows, I will describe EPA's past activities to assess and manage neurotoxicity risks, and lay out the challenges that need to be addressed in the future.

NEUROTOXICITY GUIDELINES

Test Guidelines

In order to strengthen the data base on neurotoxicity, it is necessary to have in place uniform guidelines detailing testing procedures to ensure that test data are reliable. Like other scientific disciplines, our ability to detect environmental neurotoxicants has improved over the years. When EPA was

created, the regulatory community had a limited number of tests available to detect neurotoxicants. The Agency worked hard to improve the science base and, in the early 1980s, EPA developed an initial set of neurotoxicity test guidelines to be used in the implementation of TSCA. These guidelines were developed with the help of scientists in the academic, industrial and regulatory communities and served a critical function. These guidelines constituted a peer reviewed, reliable and consistent way of testing chemicals for neurotoxic potential.

The Agency used these test methods to develop a wide variety of test data and, in the process, we improved our knowledge base considerably. Armed with this expanded knowledge base and other advances in the field we have recently completed a comprehensive revision of our neurotoxicity test guidelines. Over the last 2 years, EPA scientists from the Office of Pesticides Programs (OPP), the Office of Toxic Substances (OTS) and the Office of Research and Development (ORD) have collaborated in the revision of these test guidelines. These tests include the functional observational battery; the motor activity test; and the guideline for neuropathology studies. The OPTS guidelines are frequently cited by scientists in other agencies, academia and the public sector as a model for systematic collection of the information for neurotoxicity risk assessment. These new guidelines will permit evaluation of key neurotoxic effects, thus greatly expanding our ability to detect and assess neurotoxic hazards.

The publication of these revised guidelines is expected within the next few months.

The existing guideline for evaluating the potential of substances to cause delayed neurotoxic effects is frequently used to assess organophosphate pesticides. Delayed neurotoxicity can lead to problems with motor function (i.e. the ability to walk or move) EPA's updated guideline for delayed neurotoxicity includes a biochemical assay of the level of inhibition of neuropathy target esterase, an enzyme associated with this effect.

In addition, there are guidelines for more specialized tests. The schedule controlled operant behavior guideline discusses methods for evaluating changes in patterns of learned behavior. The peripheral nerve function guideline outlines methods for measuring the electrical activity that assures proper functioning of sensory and motor nerves.

In recognition of the greater vulnerability of the developing nervous system, in 1986, EPA began to develop a test guideline for the evaluation of developmental neurotoxicity. The guideline includes measures of learning and memory, as well as sensory and motor function in animals exposed before birth and during their early development. A workshop, jointly sponsored by the EPA and the National Institute on Drug Abuse to discuss this guideline was held in 1989. Experts from government, academia, and industry considered issues such as animal-to-human extrapolation of developmental neurotoxicity data and the ability of the

behavioral measures in the draft EPA guideline to detect neurotoxic effects in developing animals.

EPA has been active in the international community in encouraging more extensive neurotoxicity testing. In March of 1990, EPA sponsored a meeting of the Organization of Economic Cooperation and Development (OECD) Expert Group on Neurotoxicity Testing. This meeting was attended by almost 50 delegates and observers from eight member countries of the OECD. Neurotoxicity testing guidelines similar to the revised EPA test guidelines were proposed for adoption by the OECD. Incorporation of these test methods into standard toxicity evaluations used by all member countries would allow unprecedented generation of neurotoxicity information by OECD member countries. Revisions to the current OECD Guidelines for evaluation of delayed neurotoxicity induced by organophosphorus compounds were also recommended.

Risk Assessment Guidelines

EPA has been a leader in efforts to standardize the way we evaluate and interpret data in order to assess the neurotoxic potential of chemicals. The Agency is currently developing Neurotoxicity Risk Assessment Guidelines to be used across the Agency in assessing neurotoxic risks. These guidelines, which we expect to propose for public comment in 1991, are a logical extension of the neurotoxicity test guidelines. Their purpose is to guide risk assessors, risk managers, and others in the evaluation of data collected under the test guidelines and from

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other sources, as well as to inform the public on how the Agency conducts risk assessments for these effects. The guidelines will aid in determining the appropriate level of concern that should be associated with various technical findings and increase uniformity of data interpretation in various offices within the Agency.

We would like to acknowledge the strong support of EPA's neurotoxicology research program in the development of the test and risk assessment guidelines, as well as their efforts through research on many chemicals of interest to the program offices. The high quality of their research program has been an invaluable resource to the Agency in our efforts to move forward in the area of neurotoxicology.

GATHERING OF NEUROTOXICITY TEST DATA

EPA gathers neurotoxicity test data for two broad purposes: 1) to identify hazardous chemicals and, 2) to help the scientific community focus and prioritize further research into the hazards of potential neurotoxicants.

In the first instance, test data generated through the EPA Test Guidelines provides the basic data needed to determine if a chemical poses neurotoxic effects, and the parameters of these effects such as whether the effects are acute or chronic, or long lasting or transient. These data provide information so that the Agency may determine if a chemical can be used without restrictions, if special safeguards are necessary, or if the chemical should be removed from the market.

TSCA and FIFRA regulatory authority spans tens of thousands of chemical substances. Regulatory authority, economic considerations, and the availability of laboratory capacity preclude testing all chemicals for effects such as neurotoxicity. It is important, therefore, to carefully select chemicals for testing so that we reap the maximum societal benefit. In addition to helping identify hazardous chemicals, test data generated under TSCA or FIFRA help scientists identify priority candidates for further testing. For example, the data developed have helped to identify categories of chemicals with a high potential to cause neurotoxic effects (e.g., heavy metals, chlorinated solvents, organophosphorus compounds, etc.). As a result, pesticides or other commercial chemicals belonging to classes of chemicals known to cause neurotoxic effects are prime candidates for testing.

Under TSCA, there are three basic mechanisms for gathering data: data on new chemicals may be submitted under section 5; data on existing chemicals may be required under section 4; and, manufacturers must submit any data indicating adverse effects under section 8(e).

Section 5 requires that before they begin production, manufacturers of new chemicals must submit to EPA a premanufacture notification, or PMN. Although TSCA does not require manufacturers to test their substances at that time, the PMN must be accompanied by any test data that are available. If the PMN indicates that the chemicals will be produced in high

volume, or its uses would involve significant worker or consumer exposure, or discharge into air or water, EPA may require additional testing under section 5(e). One of the often required tests is based on a 28-day repeat dose test which requires neurotoxicity measures as part of the study.

Chemicals not identified for testing under one of the exposure-based criteria also are evaluated to determine whether their chemical structures are similar to other chemicals known to cause neurotoxic effects. Testing is frequently recommended on the basis of these Structure Activity Relationships (SAR).

Out of 8,382 PMNs reviewed by the Agency in the last five years, initial concerns for potential neurotoxic effects have been raised for approximately 1,200. (After further review, control action was warranted in about 10 percent of those substances.) The Agency has taken action to control risks from 74 of these substances and prohibited the manufacture of chemicals in 19 cases pending testing. In addition, 47 submissions have been withdrawn by the submitter in the face of risk concerns by EPA.

Under section 4 of TSCA, EPA can require testing of existing chemicals on the basis of either widescale exposure or chemical specific hazard. This testing has been accomplished primarily through individual test rules or consent agreements, detailing testing requirements for an individual chemical and published in the Federal Register. To date, the Agency has required neurotoxicity test data on 16 existing chemicals under TSCA. OTS first expressed concern for developmental neurotoxicity in the proposed test rule on chloromethane in 1980. Currently, OTS has

asked for this type of testing for trichloroethane and several glycol ethers.

In a major departure from the single chemical test rule, the Agency is expecting to publish, in the near future, a multi-chemical rule which proposes screening level and cognitive function tests for neurotoxicity. This will be a more streamlined approach to test rule development and is expected to obtain testing more quickly than using the traditional chemical-by-chemical approach. This approach will greatly increase the Agency's efficiency in collecting neurotoxicity data under TSCA.

In addition to data collected through TSCA test rules, EPA receives a great deal of neurotoxicity data under section 8(e) of TSCA. Under section 8(e), the Agency has received 152 submissions related to neurotoxicity studies in animals and 14 submissions related to neurotoxicity studies in humans. The Agency has also received 49 "For Your Information" animal neurotoxicity studies and 14 studies in humans that have been submitted by industry on a voluntary basis. Following up on this information, the Agency has required testing of many of these chemicals for neurotoxicity and implemented notification requirements (Significant New Use Rules) for many others.

Under FIFRA, there are also three basic mechanisms for data gathering: prior to initial registration of a new pesticide; during reregistration of older pesticides; and, under 6(a)(2), registrants must submit any data indicating adverse effects.

FIFRA requires pesticides to be registered by EPA on the basis of data adequate to demonstrate that their use will not cause unreasonable adverse effects giving the Agency wide discretion to require testing up-front. To ensure that registered pesticides meet evolving scientific standards, old pesticides are required to be reregistered, and the Agency may require registrants to conduct additional studies whenever the Agency determines it necessary to show that risks are not unreasonable. EPA has had requirements for limited neurotoxicity testing in place for many years. Testing of all organophosphorus pesticides for delayed neurotoxicity has been required since the 1970s. In addition, measurement of acetylcholinesterase inhibition has also been commonly performed for the classes of pesticides known to inhibit this enzyme, organophosphorus substances and carbamates.

EPA is nearly ready to propose extensive revisions to the pesticide data requirements, including a proposal to require neurotoxicity screening tests for all pesticides. This proposal is consistent with the recommendations of the FIFRA Scientific Advisory Panel which reviewed it in 1987. The Panel recommended that all pesticides undergo an acute and subchronic neurotoxicity battery which includes an assessment of the incidence and severity of clinical signs, an evaluation of motor activity and histopathological evaluation of nervous system tissues. The subchronic neurotoxicity study may be incorporated into the currently required 90-day subchronic toxicity study in rats. In

some cases, the neurotoxicity protocol could also be incorporated into the chronic rat feeding study.

In addition to the neurotoxicity screening battery, a number of other studies would be required under certain circumstances. The delayed neurotoxicity studies would continue to be required of organophosphorus-containing substances. Special testing of the visual system would also be proposed for organophosphates and possibly other classes of chemicals that are suspected of adversely affecting the endpoint. Developmental neurotoxicity testing also would be required on a case-by-case basis. In addition, other types of special neurotoxicity studies such as tests of cognitive function and schedule-controlled operant behavior would be required on a case-by-case basis for chemicals or chemical classes that may cause these effects.

The OTA report accurately describes the extent of testing that has been completed under TSCA and FIFRA, and I agree that the numbers thus far are small. The development and implementation of test guidelines and test requirements are very resource intensive activities. As our current activities show, we are vigorously pursuing testing under both statutes.

RISK MANAGEMENT

The Agency is currently regulating neurotoxic chemicals on a number of fronts. As noted earlier, OTS has identified 1,200 potentially toxic new chemicals, and as we have stated earlier, we have taken action to control risks from some of these substances.

Another way we can limit undesirable exposure to chemical neurotoxicants is by issuing significant new use regulations on existing chemicals if the Agency believes that new uses of these chemicals may pose an unreasonable risk. When EPA receives a significant new use notice, the Agency can then limit or prohibit manufacture of the chemical. To date, the Agency has issued proposed or final significant new use rules on 10 chemicals based on concerns for neurotoxicity.

Nearly two decades ago EPA began taking actions that reduced risk associated with lead exposures. The Agency undertook a massive effort to virtually remove lead from gasoline. Because of this and other important federal actions, blood lead levels in U.S. population have dropped dramatically. As this committee is well aware, the Agency realizes that additional reductions in lead exposure are necessary and EPA is well along on developing a comprehensive, cross-media lead strategy to establish an optimal control strategy based on reducing unreasonable risks from lead. The Agency is currently evaluating what additional steps we might take to address the continuing health and environmental risks from lead in cooperation with other Federal agencies as we have described before the committee in recent hearings.

EPA is currently exploring regulatory options for reducing risks associated with the use of acrylamide grout. Acrylamide is a known human neurotoxicant and its use in sewer grouting has been identified as presenting a high exposure potential. The Agency is at this time exploring a ban of acrylamide grout under

TSCA which will be the first time such action has been considered under TSCA on the basis of health effects from neurotoxicity.

Mercury is another agency concern which has long been associated with neurotoxicity. In the early 1970s, EPA banned all uses of mercury as a pesticide, except for a few including the use as a preservative in paints. This past summer, based on EPA's health concerns, manufacturers (registrants) of mercury products registered as pesticides for use in latex paint voluntarily agreed to eliminate the use of mercury compounds in indoor latex paint. In addition, warning labels are now required on all outdoor paint containing mercury stating that the paint is for outdoor use only.

The OTA report also identified worker protection, particularly agricultural workers, as an area needing more attention. Administrator Reilly has committed EPA to a planning process that will assign the greatest priority to problems that pose the greatest health and environmental risks. One area that has been repeatedly identified as a high priority is worker exposure.

We have undertaken a major revision of the Worker Protection Standards for Agricultural Pesticides. Final rules affecting these revisions are in the last stages of Agency review. These revisions will substantially strengthen the required workplace practices designed to eliminate or reduce worker exposure to pesticides, mitigate the effects of exposures that cannot be avoided, and improve the information and training available to

workers about the hazards of the pesticides they may encounter. Exposures will be reduced through restrictions during application of pesticides, control of workers' reentry into treated areas, and protective equipment. Improved training in pesticide hazards, and precautions and notification of pesticide applications, are expected to contribute significantly to workers understanding of hazards they may face from pesticides in their workplace and steps they should take to protect themselves.

The Agency is also considering proposing that agricultural workers exposed to pesticides be given access to Material Safety Data Sheets, or equivalent information in fact sheets tailored to the special needs of agricultural workers, describing the hazards of the specific pesticide products used on each agricultural establishment. We expect to publish such a proposal at the same time as the final rule revising the Worker Protection Standards.

The expanded testing for acute neurotoxic effects under FIFRA will also help protect the worker. Just as a driver "under the influence" of alcohol is in a risky situation, a worker "under the influence" of an intoxicating substance is in a risky situation. Impaired coordination and impaired judgement can cause accidental injury and even death. The results of acute neurotoxicity testing will allow us to design protective measures and label language to keep exposure for those who mix and apply pesticides and those who may be exposed as they work in the fields below levels which produce these effects.

Another area in neurotoxicity risk assessment that has been the focus of ongoing efforts at EPA involves regulation based on the inhibition of the cholinesterase enzyme. Roughly 35 reference doses (acceptable levels) for pesticides are based on cholinesterase inhibition. The Agency has been trying to determine whether inhibition should be regarded as an adverse effect, and if so, what level of inhibition should be considered significant. In addition, EPA has been considering what uncertainty (or safety) factors are appropriate in setting reference doses based on these effects. This issue has been considered within the Agency through its Risk Assessment Forum as well as by panels of outside experts. A workshop to review methods of measuring the enzyme is planned for next spring.

Recently, we have taken a new and wider look at the dietary risks from cholinesterase inhibitors. Since acute toxicity is the most well-established consequence of exposure to these agents, we have been evaluating risks of a single dietary exposure. This includes looking at the highest reported residues and the population consuming the largest quantities of treated commodities. We developed a novel risk assessment technique which was favorably reviewed by the FIFRA Scientific Advisory Panel. This technique represents a significant advance over our previous capabilities in this area. We are also revising our residue data requirements as a result of our experience with this risk assessment to include analysis of individual commodities which may pose these acute risks.

INTERAGENCY COOPERATION

As we have said earlier, the OTA report identifies EPA as the leader in developing test guidelines to evaluate neurotoxicity and suggests that regulatory programs from other agencies would benefit from joint test development. We welcome the opportunity to participate in such cooperative efforts. Agency neurotoxicologists actively participate in the recently formed Interagency Committee on Neurotoxicity (ICON). This committee was formed as a direct outgrowth of the OTA/EPA sponsored Workshop on Federal Interagency Coordination of Neurotoxicity Research and Regulatory Programs held in May of 1989.

The committee serves as a forum for discussion of issues of mutual interest and a source of scientific reviewers for documents in the final stages of preparation. To date, the ICON has dealt with issues such as coordination of terminology and development of a neurotoxicity data base and reviewed a draft of guidelines to be proposed by the Consumer Product Safety Commission and will hopefully become a major focus for interagency coordination in this area in the future.

CONCLUSION

As the OTA report points out, there have been extraordinary developments in the neurosciences in recent years. At EPA, much work has been done on the development and implementation of standard testing and risk assessment guidelines. New techniques in neurotoxicity screening and assessment aid in the

identification of potential neurotoxicants. This work has been very resource intensive. Now, building on this 10-year history of actively developing technical information to better understand the risks to humans from both natural and synthetic environmental neurotoxicants, increasing our in-house expertise in this complex subject, developing consistent methodology for scientific evaluation of neurotoxicity data, we are aggressively using our statutory authorities to generate additional test data and control exposure to these substances.

Testimony of

Philip J. Landrigan, M.D., M.Sc.

Ethel H. Wise Professor of Community Medicine

and

Chairman, Department of Community Medicine

Mount Sinai School of Medicine

New York, New York

Before the

Subcommittee on Toxic Substances, Environmental Oversight,

Research and Development

Committee on Environment and Public Works,

United States Senate

Washington, D.C.

October 3, 1990

ENVIRONMENTAL AND OCCUPATIONAL MEDICINE

DEPARTMENT OF COMMUNITY MEDICINE
MOUNT SINAI SCHOOL OF MEDICINE OF THE CITY UNIVERSITY OF NEW YORK
NEW YORK, NY 10029

Philip J. Landrigan, M.D.

Mr. Chairman and Members of the Subcommittee. Good morning and thank you for having invited me to appear before you today to testify on current issues in neurotoxicity.

My name is Philip J. Landrigan, M.D. I am Professor and Chairman of the Department of Community Medicine of the Mount Sinai School of Medicine of the City University of New York. I am a pediatrician, occupational physician and epidemiologist. Also relevant to my appearance before you today, I am the Chair of the Committee on Neurotoxicology and Risk Assessment convened by the National Academy of Sciences. A copy of my curriculum vitae is attached.

Background.

Injury to the nervous system caused by toxic chemicals in the environment is an important but insufficiently studied problem in public health.

The recognition that exposure to toxic chemicals may cause neurologic injury first arose from study of acute illnesses in people exposed to environmental toxicants at high doses. These illnesses included encephalopathy in children eating chips of lead-based paint, blindness in persons who had consumed wood alcohol (methanol), and coma, convulsions and respiratory paralysis following exposure to organophosphorus pesticides. Also, epidemics of neurotoxic diseases have occurred: blindness and ataxia caused by ingestion of organic mercury in fish from Minamata Bay, Japan and in fungicide-treated grain in Iraq; spinal cord degeneration and peripheral neuropathy caused by tri-ortho-cresylphosphate (TOCP) in cooking oil in Morocco and in patent medicine (Ginger Jake) in the United States; tremors, anxiety attacks and incoordination caused by the pesticide Kepone (chlordecone) in Hopewell, Virginia; and parkinsonism caused by MPTP, a contaminant of synthetic heroin in California and Hawaii. These epidemics affected tens of thousands of people, and they establish clearly that toxic chemicals in the environment can cause neurologic and psychiatric disease.

A major unanswered question, however, is whether the causal associations observed in these neurotoxic epidemics are isolated events, or examples of a widespread and pervasive association between toxic environmental chemicals and human neuropsychiatric disease. That question is one of the major unanswered issues confronting neurotoxicology today.

Subclinical Neurotoxicity.

The demonstration in recent years of subclinical toxicity adds another dimension to the issue of environmental neurotoxicity. "Subclinical toxicity" refers to the concept that chemicals in the environment, many neurotoxicants among them, may cause dose-related adverse effects at levels of exposure too low to produce signs and symptoms that are evident in the standard clinical medical examination. In the nervous system, these changes may include reduction in intelligence, impairment in reasoning ability, shortening of attention span, alteration of a wide spectrum of behaviors and fatigue. Environmental chemicals known to cause subclinical neurotoxicity include lead, organophosphate pesticides, certain chlorinated hydrocarbons, carbon disulfide, some solvent mixtures and mercury. These are compounds to which several million Americans are regularly exposed at work and to which tens of millions more are exposed generally in lesser quantities in the general environment. Although subtle in their presentation, the changes in neurologic function produced by subclinical neurotoxicity may be devastating in their effect. Moreover, because the central nervous system has little capacity for repair, the alterations of subclinical neurotoxicity may be permanent and irreversible.

The recognition of the existence of subclinical neurotoxicity raises the possibility that some undefined fraction of chronic neurologic and psychiatric illness in the American population--illnesses such as Parkinsonism, motoneuron disease, demyelinating illness and certain forms of dementia--may be exacerbated or even caused by chronic, low-level exposure to environmental neurotoxicants.

Extent of the problem.

The number of people in the American population with neurologic disease and dysfunction that may be the result of exposure to toxic chemicals in the environment is not known.

A fundamental impediment here is that the data needed to estimate the overall magnitude of the problem of environmental neurotoxicity do not exist. An evaluation undertaken in 1984 by the National Research Council, National Academy of Sciences found that relatively few of the approximately 70,000 chemicals in commercial use have ever been tested for neurotoxicity. This study found that no information was available on any aspect of the toxicity of approximately 80% of the chemical substances in commercial use. Even among the most extensively regulated classes of chemicals (pesticides, drugs and food additives), the information needed for a reasonably complete assessment of potential health hazards is available for only a minority. Also, few compounds have been assessed for their possible selective toxicity to vulnerable groups within the population such as the very young or the elderly. Moreover, there is little information available of the nature and extent of human exposure to even the materials that have been tested and identified as neurotoxic.

Given the overall low proportion of substances that have been tested for any type of toxicity, and the even smaller fraction that have been evaluated for possible neurotoxicity, it is difficult to estimate how many commercial and industrial chemicals are neurotoxic. However, there is evidence that many toxic chemicals in wide use have neurotoxic potential. Thus, of 91 criteria documents produced by NIOSH, 36 (40%) cite neurotoxicity as a reason for recommending limits on occupational exposure. Likewise, of 588 chemcials listed by the American Conference of Governmental Industrial Hygienists (ACGIH) in 1982 as both widely used in industry and as having toxicologic significance, 167 (28%) had neurologic effects as one basis for recommendations on limiting exposure.

Costs on neurologic illness.

The Health Care Financing Administration of the U.S. Department of Health and Human Services has estimated that 23 billion dollars were spent in 1980 for the care of people with diagnosed neurologic diseases. The direct and indirect societal costs of subclinical neurological losses--such as reduction in intelligence, diminution in achievement and wasted opportunity--might equal or exceed the costs of clinically recognized neurotoxic effects. If even a small fraction of the clinical and subclinical neurologic disease in the American population is caused by unrecognized exposure to toxic environmental agents, then prevention of such exposure becomes a high national priority.

Detection and Control of Exposure to Neurotoxicants.

Prevention is the key to dealing with neurological diseases of toxic environmental origin. These diseases result from exposures to synthetic and naturally occurring chemical toxins encountered in the ambient environment, ingested in foods or administered as pharmaceutical agents. Many of these diseases are not curable. They must, therefore, be prevented. They can be prevented by eliminating or reducing exposures at the source, an approach termed primary prevention. Also they can be controlled by early detection and diagnosis of neurotoxic effects while they are still reversible or while they are still at a relatively early stage of evolution when their progression may still be halted, an approach termed secondary prevention. In the prevention of neurotoxic disease of environmental origin, the single most effective approach consists of identification of neurotoxicity through routine premarket testing of all new chemical compounds before they are released into commerce and before human exposure has occurred. Prevention of disease and dysfunction is then achieved by restricting or banning the use of those chemicals found to be neurotoxic or by instituting engineering controls and imposing protective devices at points of environmental release and potential human exposure.

Given the current absence of data on neurotoxicity of most chemicals in commerce, it is clear that there is need for an extensive program of primary prevention through toxicologic evaluation. While EPA has regulatory authority to screen chemicals coming into commerce, the authority is insufficiently exercised and inadequately supported. Thus overexposures to environmental neurotoxicants can occur and people can develop neurotoxic responses to chemicals that slip through the regulatory net.

Prudent public policy must presume that all chemical substances--both those already on the market, as well as new chemicals--are potential neurotoxins. A chemical cannot be regarded as free of neurotoxicity in the absence of data on toxicity. Prudent policy dictates therefore that all chemicals, both old and new, be subjected to at least basic screening for neurotoxicity when use and exposure warrant.

A fundamental problem arises, however, from the enormous magnitude of the gap in neurotoxicity testing. Because of the great size of this problem, resources are not immediately available to undertake across-the-board testing of all chemical substances already in commerce.

Thus, new and more rational strategies for neurotoxicologic assessment of environmental chemicals must be developed. These strategies will establish testing priorities among chemicals for hazard evaluation, refine existing neurotoxicity test systems, and develop and validate efficient sensitive new testing systems and develop standardized approaches for the interpretation of test results.

The OTA Report on Neurotoxicity.

I was very positively impressed with the OTA Report on Neurotoxicity. It recognizes the existence of neurotoxicity in human populations and, additionally, the Report recognizes the potential that exists in our society for much wider extent of the problem of environmental neurotoxicity than is currently recognized. Moreover, the Report focuses on the current gap in neurotoxicity testing that I have just discussed and makes strong and reasonable recommendations for closing that gap.

The basic approach proposed in the OTA Report for testing and monitoring chemical substances consists of a tiered testing system. For the initial screening of chemical substances for neurotoxicity, the Report proposes a core battery of neurotoxicological tests, including the functional observation battery, tests of motor activity and certain neuropathological examinations. Then, for selected chemicals, secondary testing consisting of behavioral tests, tests of acute and subchronic delayed neurotoxicity and developmental evaluations. Neurophysiological evaluations may also be useful in identifying neurotoxic substances and in evaluating their adverse effects.

In my opinion all of these recommendations made in the OTA report are eminently reasonable and constitute an effective approach to the problem.

The NAS Report on Neurotoxicity.

I am not at liberty today to present to you the final conclusions of the NAS Committee on Neurotoxicity, because the report that the Committee has developed has not yet completed its passage through the very extensive review system that exists at the National Academy of

Sciences. I do, however, feel comfortable in informing you that the Committee was unanimously concerned about these issues that I have just discussed, particularly about the potential widespread existence of neurotoxicity in our society and about the fact that only a minority of chemicals in commerce have been adequately tested for neurotoxicity. In consequence of these observations, the Committee devoted extensive attention to discussing and designing approaches to the evaluation of chemicals for prevention of potential neurotoxicity in the future. I am not prepared, however, to go into those matters in detail before you today.

The NAS Committee was also very much concerned with the current paucity of epidemiologic data on environmental neurotoxicity in human populations. We therefore spent a great deal of energy discussing and developing methods for better epidemiologic surveillance of neurologic disease in human populations. In these epidemiologic studies, we gave significant attention to the possibility of including biological markers of subclinical neurotoxicity. Markers such as validated computer-based neurophysiological test batteries provide an excellent means for the early detection of neurotoxicologic injury when it is still at a subclinical stage and when further progression may be prevented.

Thirdly, while we were charged with developing risk assessement paradigms for assessing the risk to human populations of exposure to neurotoxicity, we soon came to the recognition that any assessment of risk and relation to neurotoxicants must of necessity be restricted to the most primitive stage of risk assessment, namely, hazard identification. In the current state of our knowledge, it is almost never possible to progress beyond simple hazard identification in the assessment of neurotoxicological risk. Clearly, this lack of knowledge constitutes one more potent reason as to why fundamental neurotoxicologic information on chemicals in commerce must be generated with some urgency.

Research Needs.

It is clear that research in neurotoxicity has lagged behind research in other fields of environmental science and risk assessment over the past several decades. Particularly, research in this field has lagged in relation to research in environmental cancer. That is understandable, given the great public and scientific concern about cancer, but it needs now to be rectified. Some of the best research in the United States

to evaluate human neurotoxicity and its underlying mechanisms is supported through the extramural research programs of the National Institute of Environmental Health Sciences (NIEHS) of the National Institutes of Health. This constitutes some of the most innovative and important research in the field. It will be important in the years ahead to continue to support the research programs of NIEHS and also of other government agencies that are involved in this important endeavor.

Conclusion.

I would like, in conclusion, to thank you for having invited me here before you today, and to congratulate the Office of Technology Assessment of the U.S. Congress in having done a very excellent job in developing the Report on Neurotoxicity. It is clear, readable, and cogent. It makes important points, and it makes them well.

I shall be pleased to answer any questions.

TESTIMONY OF
DR. LAWRENCE W. REITER, DIRECTOR
HEALTH EFFECTS RESEARCH LABORATORY
OFFICE OF RESEARCH AND DEVELOPMENT
U.S. ENVIRONMENTAL PROTECTION AGENCY
BEFORE THE
SUBCOMMITTEE ON TOXIC SUBSTANCES, ENVIRONMENTAL OVERSIGHT, RESEARCH AND DEVELOPMENT
COMMITTEE ON ENVIRONMENT AND PUBLIC WORKS
UNITED STATES SENATE

OCTOBER 3, 1990

I. Introduction

Mr. Chairman and members of the Subcommittee, I am Lawrence Reiter, Director of the Health Effects Research Laboratory, in the Office of Research and Development, at the U.S. Environmental Protection Agency (EPA). I want to thank you for the opportunity to appear before you today to briefly describe the health research program at EPA, outline the goals, current scope, and future directions of the neurotoxicology program; and provide comments on the Office of Technology Assessment's (OTA) study titled Neurotoxicity: Identifying and Controlling Poisons of the Nervous System.

EPA is responsible for safeguarding public health from the adverse consequences of exposures to environmental agents. To accomplish this mission, EPA must be both a regulatory agency and a science agency. As a science agency, EPA carries out relevant and timely research to ensure that Agency decisions are based on sound scientific information.

EPA is in a unique position to plan and carry out an environmental research program that assimilates and builds on related

work of other federal agencies, as well as in the scientific community. The EPA health research program is specifically designed to provide scientific data that will improve Agency decisions about the protection of public health. The emphasis is on developing an adequate understanding of the relationship between pollutant exposures at environmental concentrations and related human health effects. Because a stronger scientific foundation for risk assessment is the key to more informed decisions about safeguarding public health, our research program focuses on improving the quality and the quantity of relevant health information used in the risk assessment process. To support the Agency's risk assessment process, the Health Effects Research Laboratory performs three types of research. First, it develops, refines and validates methods for identifying cause and effect relationships between environmental pollutants and adverse health outcomes. Particular attention is given to developing techniques that are faster, more accurate, less expensive and more reliable than those currently used.

The second type of research deals with the development of predictive models for clarifying the relationships between pollutant exposure, how much of the pollutant gets to the critical site in the body, and the resulting human health effects. The major goal of our predictive models research is to develop biological information of the movement of a chemical through the body and on the physiological and biological mechanisms responsible for toxicity. These models are critical to reducing the uncertainties in the risk assessment process, thus eliminating the "fall back" or "default" positions

currently used by risk assessors. As it now stands, different groups, applying different default positions, can arrive at diametrically opposite risk assessment conclusions from the same data.

The third type of research is to develop specific scientific data on individual pollutants at the request of the regulatory offices. The health research program is structured so that methods and models developed or utilized by the Health Effects Research Laboratory can be applied to the collection of toxicological data using laboratory animals and/or human clinical and epidemiological data.

The Health Effects Research Laboratory is located in Research Triangle Park, North Carolina, and has approximately 280 employees of which over 120 hold advanced degrees. Contractor personnel are used to augment the program and provide facilities support. By conducting research across multiple levels of biologic organization ranging from molecules, to cells, to individual organisms, to populations, the laboratory gains a more complete understanding of the physiologic and biochemical mechanisms that underlie chemically-induced disease. Because environmental exposures can result in a wide range of human health effects, EPA scientists currently study the pulmonary, cardiovascular, genetic, reproductive, developmental, immunologic, renal, hepatic and neurotoxic effects of pollutants. The diversity of scientific expertise in the Health Effects Research Laboratory make it one of the most comprehensive environmental health facilities in the world. As the only health

research laboratory in EPA, we perform research in support of all major legislation for which EPA is responsible.

II. Neurotoxicology Research

A. Need for Neurotoxicological Research

We are concerned that human exposure to neurotoxic agents may be significant because a wide variety of physical and chemical agents, including radiation, plant and animal toxins, metals, solvents and pesticides have been demonstrated to have neurotoxic effects. For example, many active pesticide ingredients registered by the Agency are known to be neurotoxic. The Office of Technology Assessment (OTA), in a 1984 report to Congress, estimated approximately one-fourth of the chemicals frequently encountered in industry with toxicologic significance may be neurotoxic. In a report on toxicity testing requirements it has been estimated by the National Academy of Sciences that inadequate toxicological information exists for hazard assessments on 78% of the nearly 13,000 commercial chemicals with production volumes in excess of 1 million pounds per year. If it is assumed that one-fourth of these chemicals may produce neurotoxicity, then there are an estimated 2,500 chemicals being produced at approximately 1 million pounds/year with undefined neurotoxic potential.

The Neurotoxicology Division serves as the focal point for planning, conducting and evaluating research to improve our understanding of and ability to predict the effects of environmental chemicals on the adult and developing nervous system. This Division was created in 1978 when EPA and the Food and Drug Administration

signed an interagency agreement combining two groups, one at each Agency. Today our program is the largest, most comprehensive neurotoxicology program in the world, having the unique ability to evaluate neurotoxicity at all levels of neurobiological organization and to study neurotoxic effects in both laboratory animals and humans. The division has approximately 70 scientists and technical support staff, including 24 individuals holding advanced degrees. In addition, students and postdoctoral fellows are trained at the Neurotoxicology Division through arrangements with the National Academy of Sciences and local universities.

B. Current Research Program

The Neurotoxicology Division's research focuses on the development, refinement and validation of methods to screen and characterize the effects of neurotoxicants. Validated methods are then used to generate predictive models and quantify public health risks. In addition, validated test procedures are also used to provide data on specific chemicals, or chemical mixtures, of interest to the Agency.

1. Methods Development: As with other areas in toxicology, neurotoxicology requires the development of a variety of test methods that can detect, quantify and characterize effects following exposure to chemical, biological or physical agents. In humans, pollutants may alter motor functions such as strength and coordination, sensory functions such as vision or hearing, cognitive functions such as learning and memory, and autonomic functions such as regulation of body temperature. The Neurotoxicology Division studies the effects

of chemicals on these functions at all levels of neural organization, including neurobehavioral, neurophysiological, neuroanatomical and neurochemical. Such studies utilize methods derived from experimental psychology, electrophysiology, pharmacology, biochemistry, cell and molecular biology. Our research goal is to develop valid methods for detecting and quantifying the neurotoxicological effects of chemicals and to eventually be able to predict a pollutant's neurotoxicological properties based on an understanding of its chemical structure.

The Neurotoxicology Division has made significant scientific contributions in the area of methods development and validation. It has provided methods and technical guidance to the Agency for several developmental and adult neurotoxicity testing guidelines. Industry in the United States are beginning to routinely use these protocols, thus allowing the Agency to obtain standardized data from different laboratories which greatly advances data interpretation. A subset of these guidelines is under consideration for use by countries associated with the Organization of Economic Cooperation and Development. Research performed by the Neurotoxicology Division has also led to the development of a battery of neurological tests currently used by laboratories throughout the United States; these tests are also being standardized and validated for use internationally under the auspices of the International Programme for Chemical Safety of the World Health Organization.

In the future, the Neurotoxicology Division will focus on the development of test methods that rely on <u>in vitro</u> or tissue culture

procedures and on techniques designed to detect neurotoxicity based on neurotoxic mechanisms of action. Such advances are needed to improve the rate at which chemicals can be assessed. When applied to the study of complex questions such as those associated with the neurotoxicity of chemical mixtures, these short-term methods will reduce the cost and number of animals required for screening.

2. Predictive Models: The second major research emphasis in the Neurotoxicology Division concerns the development of predictive models. A major goal of this research is to reduce the uncertainties associated with extrapolating from the higher doses frequently used in toxicological studies to exposure conditions normally encountered by humans. Current research at the Nuerotoxicology Division is focusing on the development of models which are environmentally relevant and on studies leading to identification of a chemical's possible mechanisms of action. This information is critical to understanding the relevance of an observed effect to actual human health risk.

An important aspect of our model development research is identification and evaluation of populations that show an unusual susceptibility to pollutant exposure. For example we know that children are more susceptible than adults to the neurotoxic effects of some chemicals, such as inorganic lead. Some of the Neurotoxicology Division's most significant work led to a better understanding of the health effects of low level exposure to metals and pesticides in the very young. This work has been the cornerstone

in the study of developmental neurotoxicity in animal models which have application to both the fetus and the child.

Future research in the Neurotoxicology Division will focus on other possible susceptible populations, particularly the aged, and on the consequences of long-term, low-level exposures to neurotoxic agents. Of particular interest are the possible neurotoxic effects that may follow repeated exposure or that may appear following cessation of exposure. The Neurotoxicology Division has observed, for example, that tolerance as indicated by some symptoms, may develop after repeated exposure to certain enzyme inhibiting pesticides, such as the widely-used organophosphate insecticides. Other effects, however, such as short-term memory loss, appear to worsen with repeated exposure.

3. Chemical Specific Data: In the course of performing risk assessments, the Agency is often confronted with the need to obtain additional information on specific chemical pollutants. Over the last decade, the Neurotoxicology Division has provided significant information on neurotoxicity produced by over 100 chemicals including urban and indoor air pollutants, drinking water contaminants, pesticides, metals and solvents. This research has helped the Agency make regulatory decisions and provided fundamental insights into the mechanism by which these environmental pollutants adversely affect the nervous system. A major accomplishment has been improved understanding of the neurotoxic effects of organophosphate pesticides. This research enabled the Office of Pesticides and Toxic Substances to revise its testing guidelines for this particular

pesticide class and has lead to revision of the proposed testing guidelines of the Organization of Economic Cooperation and Development.

In summary, the Neurotoxicology Division is internationally recognized for its expertise and ability to perform high quality, relevant and timely research. Scientists in the Division are frequently involved in organizing and planning national and international meetings on neuroscience and neurotoxicology. In addition, they present scientific papers, serve on editorial boards of major scientific journals and are active in academic training of university students and postdoctorals.

III. Future of Neurotoxicology

The importance of neurotoxicology will continue to grow in the future. Twenty years ago, the Society of Neuroscience had less than 500 members; today it has nearly 19,000. These figures reflect the increasing and intense scientific interest in unraveling the mysteries of the nervous system. In fact, Public Law 101-58 recently declared the 1990's to be The Decade of the Brain.

Despite recent developments and events in neurotoxicology and neuroscience, considerably more research needs to be done. For example, the number of environmental agents that could adversely affect the nervous system is large, and most have not been evaluated for neurotoxicity. Many scientists are concerned that whole-animal screening methods may not be cost-effective in assessing such a large number of agents for potential neurotoxicity. Although *in vitro* or tissue culture techniques have been used to a limited degree in

neurotoxicology, research to develop, refine and validate such procedures will be needed before they can be routinely applied to neurotoxicity assessments.

Biologic markers that provide evidence of exposure or effects from chemical agents are an important goal for regulatory toxicology. Development and validation of biomarkers are important research needs because of the potential for biomarkers to serve as early indicators of pollutant exposure, neurotoxic effects, or susceptibility.

One of the major thrusts in neurotoxicology for the future will be in the area of risk assessment. There is an obvious need to generate high quality neurotoxicant dose-response data and to perform research to reduce uncertainties associated with the use of currently available methods and animal models to predict human risk. Of particular interest are a number of extrapolation issues, including brief versus repeated or intermittent exposure, high level exposure to low level exposure, route-to-route and animal to human. All of these extrapolation issues limit the precision of current risk assessment and need to be studied more thoroughly.

Some environmental agents and naturally occurring substances can effect the nervous system and result in neurodegenerative disorders that are similar to amyotrophic lateral sclerosis (Lou Gehrig's disease), Parkinsonism, and Alzheimer's-like diseases. Further research is needed to identify links between environmental exposure to chemicals and the development of progressive neurodegenerative diseases.

In addition to these general neurotoxicological research needs, there is also a need to develop a data base for the hundreds of known neurotoxicants in the environment. Such a data base would lead to more rapid and precise determination of the risk associated with neurotoxic exposures. Some classes of widely used chemicals, such as the cholinesterase inhibiting pesticides used throughout the world, deserve special attention. In spite of their wide-spread use, there is no common agreement as to a biological endpoint that should be used to perform risk assessments for these agents. In addition, little is known about their effects on the fetus or child or about the effects of repeated low level exposure on cognitive function.

In summary, neurotoxicology has moved into the mainstream of environmental toxicology. Nevertheless significant gaps exist in our knowledge of how to measure and quantify the risk associated with exposure to potential neurotoxicants. Advances in the state of the science in toxicology and in the neurosciences must be integrated into the discipline of neurotoxicology if we are to be successful in reducing these uncertainties.

IV. Comments on the OTA Report

The OTA report identifies a number of important policy issues concerning the adequacy of the current Federal research framework for addressing neurotoxicity, the need to improve interagency coordination of Federal neurotoxicology research, and the need for international research cooperation in neurotoxicology.

A clear underlying theme in the OTA document is that neurotoxicology should receive more research attention. We agree,

and in fact, I have already identified some areas that will require further research. To address these research needs adequately EPA must cooperate closely with other government agencies as well as the academic and industrial scientific communities. EPA will continue to perform research that improves the neurotoxicity risk assessment process. As I mentioned previously, the development and validation of in vitro tests, improvements in our ability to predict the likelihood of neurotoxicity based on chemical structure and properties, and a better understanding of how chemicals produce damage to the nervous system are necessary before the key uncertainties can be significantly reduced.

In addressing these research needs, it is appropriate for EPA to involve a wide spectrum of the scientific community. Because we understand the regulatory needs of the Agency, needs that are often common to other regulatory agencies, we feel that EPA's neurotoxicology program has a unique leadership role in identifying and overseeing important areas. Cooperative research ventures can be useful and efficient. Often, the cooperative research agreements between EPA staff and investigators in the outside scientific community serve to enlighten academic scientists as to the regulatory needs of the Agency and therefore produce data that is more useful for regulatory activities.

Maintaining and strengthening interagency coordination of neurotoxicology research is critical to ensuring an efficient and productive Federal effort. The Neurotoxicology Division currently has a leadership role in interagency coordination. The Interagency

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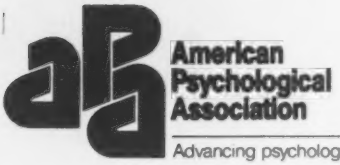
Committee on Neurotoxicology (ICON) developed from a workshop on Federal interagency coordination co-sponsored by EPA and OTA. The ICON, which is currently chaired by Dr. Hugh Tilson, Director of the Neurotoxicology Division, is comprised of 22 representatives from seven different Federal agencies. The committee has already drafted a consensus definition of neurotoxicity (a previously contentious issue both inside and outside the regulatory agencies), and has recently begun to explore new approaches to quantitative risk estimation. Currently, the ICON is effective because the leading Federal scientists have been willing to work together towards a more coordinated approach; however, continued success will depend heavily on the priorities in each of the participating organizations.

As the OTA report noted, neurotoxic effects are not unique to the United States. For many years, EPA has played a leadership role in international activities related to neurotoxicology. The Neurotoxicology Division is currently the lead laboratory coordinating an international, interlaboratory comparison study for the World Health Organizations's International Programme on Chemical Safety. The purpose of this study is to standardize and validate a neurobehavioral screening battery. The Neurotoxicology Division is also a key participant in an Organization of Economic Cooperation and Development (OECD) activity to develop a neurotoxicity testing protocol for use by its member countries. This protocol is very similar to the one recently prepared by EPA's Office of Pesticides and Toxic substances with the Neurotoxicology Division's collaboration. We have benefited considerably from our limited

international involvement. In light of recent developments, we feel that EPA as well as other government agencies would have much to gain from continuing and expanded international involvement. For example, in Eastern Europe, where the scope and severity of environmental pollution is just becoming evident, unique opportunities arise for answering some longstanding questions using carefully designed studies. The Neurotoxicology Division believes that fostering international cooperation in research and information exchange will benefit all countries involved immeasurably.

In summary, we agree with the OTA's report that exposure to potential neurotoxicants in the environment may pose a significant threat to human health. Neurotoxicological research in government, academia and industry has entered into the mainstream of both the larger disciplines of toxicology and neuroscience. The Neurotoxicology Division at the Health Effects Research Laboratory has a trained cadre of neurobiologists and neurotoxicologists responsible for conducting relevant and timely research to provide the scientific data necessary for appropriate regulatory and enforcement decisions. Many fundamental questions concerning neurotoxicology remain to be answered and much work needs to be done.

This concludes my statement, Mr. Chairman. I will be happy to answer any question you or the Committee members may have.



Advancing psychology as a science, a profession, and as a means of promoting human welfare

TESTIMONY OF

RONALD W. WOOD, PH.D.

Research Associate Professor

New York University Medical Center

on behalf of

THE AMERICAN PSYCHOLOGICAL ASSOCIATION

before the

UNITED STATED SENATE

Committee on Environment and Public Works

Subcommittee on Toxic Substances, Environmental Oversight,
Research and Development

on the subject of the

OFFICE OF TECHNOLOGY ASSESSMENT'S REPORT

"Neurotoxicity: Identifying and Controlling Poisons of the Nervous System"

October 3, 1990

The Honorable Harry Reid, Chair
458 Senate Dirksen Office Building

1200 Seventeenth Street, N.W.
Washington, D.C. 20036
(202) 955-7600

Mr. Chairman, Members of the Subcommittee, I am Dr. Ronald W. Wood, Research Associate Professor of Environmental Medicine at the New York University Medical Center. I am here on behalf of the American Psychological Association (APA), a scientific and professional organization representing over 102,000 psychologists. I am also President-Elect of APA's Division of Psychopharmacology, whose members include those psychologists most concerned with the effects of chemicals, medicines, and drugs on behavior and the function of the nervous system. I want to thank you for the opportunity to testify on the Office of Technology Assessment's (OTA) report, "Neurotoxicity: Identifying and Controlling Poisons of the Nervous System."

For over 10 years I've been chairman of an APA committee which has been following and commenting on the activities of the Environmental Protection Agency (EPA) as it has tried to cope with behavioral neurotoxicity issues. It has been a decade of frustration and disappointment for those of us who looked to EPA for leadership in confronting these complex problems.

This Subcommittee, on the other hand, has recognized the importance of research and testing in the regulatory process -- as your recent amendments to S. 2006, "The Department of the Environment Act of 1990," demonstrate. Without information on hazardous substances, or an effective mechanism to collect such information, we will be condemned to study the aftermath of one industrial accident or mass health disaster after another. Today, I would like to focus attention on our national failure to identify the non-cancer

hazards of chemical exposure. This broad issue is a problem highlighted throughout the recent OTA report on neurotoxicity.

The resolution to the serious problems with the regulation and control of neurotoxic substances (described in the OTA report), will require the implementation of many of the policy and legislative options outlined in the first chapter of the OTA report. I would like to point out that although the OTA report focuses on neurotoxic effects, the problems it describes with the research and regulatory system also apply to the other adverse health and environmental effects (i.e. cardiovascular, immunological, developmental) which can result from chemical exposure.

Two crucial components of any strategy to protect the public's health, and the environment, are: 1) ensuring the availability of toxicity information; and 2) effectively implementing the Toxic Substances Control Act (TSCA). I will now speak to our nation's failure to generate this needed toxicity information, and its failure to fully implement TSCA.

Identifying Hazards to Health: Who Does It?

Unfortunately, we cannot always rely on free market mechanisms to produce the information necessary to protect the public's health. The President's Council of Economic Advisors recognized this when they stated in their 1990 annual report:

"...Environmental problems arise in market economies when private individuals and businesses lack incentives to take full account of the environmental consequences of their actions...The private market does not always produce the information needed to solve public problems. Private firms typically do not realize profits from research and development aimed at understanding environmental processes or the relationship between pollution and human health. Government action is often necessary to produce such information to further public policy objectives...These market failures...provide a rationale for government action..." (p. 188).

Chapter 4 of the OTA report discusses in some detail the roles of industry, academia, and the government in promoting toxicology research, education, and toxicity evaluations.

Industry

With the exception of pesticide manufacturers, even public-spirited, responsible corporate leaders do not regard their toxicology research as profitable. The industrial toxicologist is employed to control liability costs and to satisfy regulatory demands. It is an unusual company that supports a state of the art toxicity program. Some companies do participate in research consortia that examine commodity chemicals or problems of specific concern to several companies. Much of the resulting information never sees the light of day, however. It's confidentiality is protected by

its corporate sponsors -- and this is a terrible waste. Regulations and incentives should be created so that industry will not only generate toxicity information, but also make it publicly available. This is their moral obligation, and it should be their legal responsibility as well.

Academia

Universities serve not only to educate, but to provide the setting for much of the nation's basic research. There are few universities, however, that have the critical mass of neurotoxicologists necessary for the multidisciplinary efforts which are most likely to produce the needed data on neurotoxicity. Such a critical mass could be achieved by targeted funding programs to create centers of research excellence. Training and research funds for neurotoxicology are inadequate. The EPA Administrator, the Director of the National Institutes of Health (NIH), the Alcohol, Drug Abuse and Mental Health (ADAMHA) Administrator, and the Director of the National Institute of Environmental Health Sciences (NIEHS), should be asked how they plan to foster the necessary research and training programs in neurotoxicology and behavior.

University researchers operate under work under the joint demands of their academic departments and funding agencies to produce high quality, basic research. The kind of research needed to generate toxicological data is "applied" and generally does not achieve as much respect or attention as "basic" research. Add to this the lack of money to support the generation

of toxicological data, and it is easy to understand the dearth of such data. Academic researchers will not evaluate the safety of proprietary chemicals unless the chemical serves as a tool to help explore the structure or function of the body, or to understand the mechanisms of toxicity. Universities deserve more support for the important role they play in performing what little toxicological research there is, but they cannot perform all the necessary research and testing needed to protect the public's health.

Government

Research on neurotoxic effects are highly fragmented and dispersed across government agencies. The OTA report discusses in detail the problems generated by this fragmentation. There was hope that elevating the EPA to cabinet status might result not only in an enhancement of targeted research and training programs, but also in better coordination between EPA and other regulatory agencies such as the Food and Drug Administration (FDA), the Consumer Product Safety Commission (CPSC), the National Institute for Occupational Safety and Health (NIOSH), and the National Institute of Environmental Health Sciences (NIEHS). That hope has diminished since the legislation to elevate the EPA to cabinet status has stalled.

Providing for the generation of the necessary toxicity data is necessary to ensure the public's health and protect the environment. The effective implementation of existing legislation -- TSCA -- is necessary to do this.

The Toxic Substances Control Act

The APA Division of Psychopharmacology's Committee on Neurotoxicity that I chair, was optimistic when the EPA was given the responsibility for administering TSCA. This was an opportunity for the nation to improve its knowledge about the neurobehavioral toxicity of chemicals, and to help protect the public from the risk of injury. Our committee wanted to ensure that the required testing was done properly, and we provided comments on test methods. Imagine our dismay over the years as it became evident that despite TSCA, the required testing was not being done. As we gained experience with the testing process, we commented repeatedly on proposed test rules, and also suggested the testing of particular chemicals that we judged in need of immediate examination.

To give an example, the phenylenediamines, a set of chemicals used in some hair dyes, were put on the EPA's priority list in 1980. EPA's review process did not suggest much concern about the neurotoxicity of these chemicals when they proposed a test rule 2 years later in 1982. Our committee did a more thorough review and became very concerned because some

of these compounds produced seizures in animals. These seizures were sometimes seen within half an hour of placing a few drops (0.2 ml) on the animal's backs. There was also evidence dating back to 1932 of human nervous system disturbances after the use of hair dyes that were only relieved by shaving the scalp. Our comments in 1982, 1986, and 1988 were not completely ignored -- a test rule was finally issued that addressed our concerns on November 30, 1989. This was 9 years after the chemicals were placed on the EPA's priority list.[1] These compounds obviously disturbed nervous system function, but it took nearly a decade to issue a test rule. How long would it have taken to get testing underway if gross effects had not been obvious?[2] Frustrated by a series of similar experiences, our committee turned its attention from the particulars of individual regulatory actions to the broader issues of process, research and testing needs, the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) legislation, and research appropriations.

Improving TSCA

These long delays are just part of the problem with TSCA, which has severe structural defects. These defects apply to all of the health and

1. I would be happy to provide the Subcommittee a record of the forgoing activities, if requested.
2. See section, How Bad is the Problem?

environmental concerns TSCA was designed to address -- not just neurotoxic and behavioral effects. Even with well intentioned, hard working, and public spirited leadership, a broken mechanism cannot deliver the goods. This Subcommittee recognized the problems with TSCA in the mid-80's as the 98th Congress considered several bills that would have changed TSCA.[3] Some of the suggested improvements in these previous efforts to amend TSCA are still applicable today:

- Establish as the intent of Congress that those who manufacture and process chemicals, "...have a duty to be informed about the toxic effects of such chemical substances and mixtures and to take appropriate actions to prevent exposures that might be harmful to human health or the environment..."[4] Under current law, manufacturers are only responsible to pay for the cost of testing if EPA can argue that testing is "necessary." Thus EPA spends public resources arguing about testing with manufacturers, and generates relatively little information.

- To deal with new chemicals, 2 suggestions are offered: 1) establish a base set of toxicity information on all new chemicals, similar to that required by the Organization for Economic

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3. S. 3075, H.R. 4303, and H.R. 4304, all introduced in the 98th Congress.
4. S. 3075, 98th Congress.

Cooperation and Development (OECD). Currently, the collection of toxicity information is not required -- it need only be submitted if it exists; and 2) have EPA order simple, early toxicity tests of new chemicals (or do them itself) rather than carrying the administrative burden of conducting discussions with, and inducing compliance from, manufacturers.

- Use the volume of chemicals produced as a testing trigger, since volume produced is a crude estimate of the population exposed to a chemical and any of its potential, harmful effects. Not all high volume chemicals will require testing (as adequate information may already exist) and it could be left to the discretion of the EPA Administrator.

- Make the Interagency Testing Committee (ITC) a center of regulatory action, and a central focus of toxicity evaluation activity in the federal government. Currently, chemicals identified by government agencies as in need of testing are usually referred to the National Toxicology Program (NTP) where they may be evaluated at taxpayer expense. Toxicity testing of commodity and specialty chemicals should be borne by the manufacturers and users, not the taxpayers at large. The public should pay for studies of non-proprietary, non-commercial chemicals such as: diet constituents; drugs of abuse; orphan medicines; combustion products; smog and its constituents; heavy

metals, and so forth. The channeling of testing candidates through the ITC, could save taxpayer dollars by efficiently coordinating the requests for NTP testing and making it the testing agency of last resort.

- Eliminate the duplicative review of chemicals by both the ITC and the EPA's Test Rules Development Branch. Public access to this review information should also be enhanced, and notices filed as currently required. Negotiated testing, or "consent orders," should be encouraged. In the absence of prompt notification (90-120 days) that testing has commenced by the manufacturer, EPA should have the power to commence testing. This testing could be done under the National Toxicology Program, or through contracts. The cost of EPA's testing could be assessed as the cost of testing plus management expenses, and could be paid for by the manufacturer. This would produce a monetary incentive for the manufacturer to generate the information in a timely manner, or else have to reimburse EPA's testing costs.

- Superfund provides a model for the generation of financial resources to both pay for the testing, and the methodological research needs of the toxics program. Unlike the Superfund, however, these monies would be used to <u>prevent</u> health and environmental disasters -- rather than to clean them up after they have occurred. This new Chemical Safety Fund could be created by

assessing the manufacturers of the highest volume chemicals from which other chemicals are made (i.e. feedstock chemicals), a very small fraction of the value of their products. Since these starting chemicals are then distributed throughout the economy and made into other chemicals, consumer products, fuels and such, the funding of the testing program would be tied loosely to the volume of chemicals that are generated and released into the environment.

When a testing need arises that is not being met voluntarily or promptly by industry, the testing could begin with money from this fund -- much like the cleanup of hazardous wastes are charged to the Superfund until charges can be collected from the responsible parties. The cost recovery would be much better under this proposed model, however, as it would be clear who is responsible for the manufacture of currently produced chemicals. Testing could be performed under the auspices of the NTP, or through contractual mechanisms. In this way, both the public's health and the environment would be protected expeditiously, while the bills are collected from those who profit from the chemical's manufacture.

In addition, some funds could be drawn from the proposed fund to support research activities relevant to its purpose -- as is now done with Superfund money. This money could be used to help support the extramural and intramural research programs of EPA which have been profoundly underfunded for the past 10 years.

How Bad is the Problem?

- The OTA report tried to estimate the economic benefits of regulating neurotoxic substances, and performed a conservative analysis recognizing direct and indirect benefits and savings. Focusing on just one type of mental disorder, drug-induced dementias, OTA provided a lower bound estimate of $500 million to $1.5 billion. Similarly, the health benefits of reducing the neurotoxic effects of lead exposure from automotive exhausts were placed at more than $500 million annually between 1986 and 1988. The most recent data available (1980) on the national annual direct costs for personal health care estimate that approximately $40 billion were spent on mental disorders, and diseases of the nervous system and sense organs, ranking third and fifth in the list of most expensive medical conditions. These estimates excluded lost productivity, restricted activity costs, and other rehabilitative costs. Thus, the economic costs of neurotoxic poisoning may be substantial. Not factored into this analysis is

the cost of human suffering and loss of quality of life caused by neurotoxic poisoning.

- In 1984 the National Academy of Sciences conducted a major study, Toxicity Testing: Strategies to Determine Needs and Priorities. It found that for the 90% of manufactured chemical that are in commerce (approximately 45,000), 90% of these had minimal or no toxicity information available. The study concluded that neurobehavioral toxicity testing was one of the highest priority testing needs.

- Of the 588 chemicals for which the American Conference of Governmental and Industrial Hygienists have set occupational exposure limits, neurobehavioral effects were of concern for approximately a third.

- EPA estimates that 14,000 of the 65,000 chemicals on their inventory warrant prompt examination.[5]

- The Government Accounting Office (GAO), in their report Toxic Substances: EPA's Chemical Testing Program Has Made Little Progress (April 1990), describes a bad situation. The interagency

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5. Testimony of Linda Fisher, EPA on 6-20-90.

Testing Committee (ITC) is charged with generating a list of chemicals to be given priority consideration for testing by the EPA Administrator. As long ago as 1980, EPA and the ITC identified 2,226 chemicals that they thought might be harmful, and that deserved in-depth review. However, the ITC succeeded in bringing only 386 chemicals to its list in the 13 years covered by the GAO report. This is an average of 32 per year. The current rate of nomination is much lower though, as over 300 of the chemicals on the list appeared there before 1980! This potentially important process needs immediate repair.

- Of the chemicals which are on their priority list, EPA has decided that 25% do not warrant testing (testing is already underway, there is a limited production volume, or data already exists). For the remaining chemicals, EPA typically takes about a year to review the chemicals and to issue a proposed test rule. It can then take another 27 months to issue a completed test rule. Testing then commences, taking 2 to 5 years. According to the GAO report, EPA did not begin receiving such test results until May of 1988. By the end of fiscal 1989, EPA had received complete test data for only 6 chemicals, and has not finished deciding what action to take -- if any. If EPA could succeed in generating test

data on just 20 chemicals per year (a vast improvement over the current rate), it would still take 700 years to deal with the 14,000 chemicals over which they've expressed concern. This process needs to be streamlined.

I hope that my testimony today has adequately expressed how concerned the scientific community is about the current state of testing and regulation of neurotoxic substances. This is a serious problem whose consequences may haunt us for generations. I want to thank the Subcommittee for its attention to, and consideration of, my remarks. I will be happy to answer any questions you might have.

TESTIMONY AT A HEARING OF THE SUBCOMMITTEE ON TOXIC SUBSTANCES, ENVIRONMENTAL OVERSIGHT, RESEARCH AND DEVELOPMENT ON OCTOBER 3, 1990

By Ruth E. Billings, Ph.D.
University of Nevada Medical School

SUMMARY

* Despite the efforts of many agencies the population continues to be exposed to toxic chemicals

* Part of the reason for this exposure is that complete hazard assessment is available for less than 1 per cent of commercial chemicals.

* However, generation of this data for the 65,000 chemicals in the Environmental Protection Agency (EPA) inventory would require huge resources and would cost over one million dollars per chemical.

* Thus, it is essential to restrict detailed testing to those chemicals which have a high probability of showing toxicity.

* The selection of chemicals for detailed study must be based on simple tests which model chronic exposure to the substance. Unfortunately, few such suitable procedures are available.

* Increased industry-EPA cooperation might provide a stimulus to generate needed information without burdening industrial development or risking disclosure of proprietary information.

* Federal regulatory agencies need to communicate more closely and eliminate duplication of effort.

* Scientific research within Federal regulatory agencies should be examined to eliminate duplication and to determine if such studies would be more effectively carried out in traditional research organizations such as NIH or universities.

* Regulatory decisions should be based on scientific data and the interpretations of such data by scientists. Where consensus opinion is presented, a regulatory body should be

* Innovation in toxicology needs to be stimulated to develop the scientific knowledge of the cellular/molecular basis of chemical toxicity. This information is essential for the development of the needed novel, simpler toxicity tests.

* Diminishing Federal research grant funding is having a negative impact on technology development in toxicology.

The desirability of protecting the world's population from toxic substances in the workplace, at home and in the environment is undebatable. The debate is how to attain maximum protection and minimize risk without jeopardizing technological advancement. In spite of our explicit concern, including the enactment of more than a dozen Federal laws regulating toxic substances, the public continues to be exposed to toxic substances, and to suffer adverse health effects as a result. The Office of Technology Assessment (OTA) document under review today (Neurotoxicity: Identifying and Controlling Poisons of the Nervous System) lists seven major neurotoxicity incidents since 1970. Included in this list is the poisoning in 1980 of workers in a plastic bathtub manufacturing plant. These workers were exposed to a neurotoxic hexane derivative, BHMH, even though n-hexane has been known since the early 1970's to be neurotoxic. The National Academy of Science (1989) recently reported that 12 percent of children under 18 in the United States have one or more mental disorders and identified exposure to toxic substances as one of the risk factors.

IMPORTANCE OF TOXICITY TESTING TO RISK ASSESSMENT

It is readily apparent that we must do a better job of identifying hazardous chemicals and limiting exposure through risk management. To establish appropriate safety standards and licensing of chemicals, and thereby minimize public health risks, requires information about the properties and mechanisms of action of potentially toxic substances to which humans may be exposed. Thus toxic substance control is dependent upon scientific data. These data must be obtained from toxicity tests of individual chemicals. The usefulness and applicability of the test data are only as valid as the testing procedures themselves. A complete set of toxicity tests, such as routinely required for drug licensing applications includes at least a dozen major studies in which multiple animal species and both sexes are dosed with the experimental drug for varying lengths of time (one dose to lifetime exposure). Many parameters of toxicity are measured, including, teratogenicity, carcinogenicity, and reproductive effects as well as gross behavioral changes and histopathological alterations. This extensive list of toxicity tests is required for a single chemical because we know that chemicals have a very specific profile of toxicity (i.e. only specific organs and/or cell-types

are affected). In addition, there is considerable variation between animal species and sexes in susceptibility to toxic chemicals. For example, a chemical may have neurotoxic effects in male mice, but not in female mice or male rats. The application of this comprehensive testing paradigm would be ideal, but it is impossible, from a practical point of view, for the estimated 65,000 chemicals which are in the Environmental Protection Agency's (EPA's) inventory alone. A National Academy of Science (1984) report estimates that a complete health hazard assessment is available for less than 1 per cent of commercial chemicals and toxicity information is totally unavailable for 80 per cent. Nervous system toxicity has been studied in detail with only a few chemicals (OTA report).

TOXICITY TESTING IS RESOURCE LIMITED

The paucity of toxicity information for the majority of environmental chemicals, in particular, is understandable and somewhat justifiable when the resources required for toxicity testing are considered. The standard test for carcinogenicity, for example, involves life-long observation of rats and mice, takes three to five years to complete, and costs nearly a million dollars per chemical tested. It has been estimated that world wide, only about 300 chemicals can be introduced into testing facilities each year (Lave and Upton, 1987). This is far less than the number of new chemicals introduced, without considering the backlog of existing chemicals which have not been tested. Complete neurotoxicity testing, including subchronic and chronic administration protocols, is estimated to cost more than $300,000/chemical and require more than 2-years for completion (OTA report).

NECESSITY OF PRIORITY RANKING OF CHEMICALS

A priority ranking of chemicals to be tested is essential. Criteria and strategies for setting priorities include a sequential protocol that starts with relatively inexpensive, and rapid screening tests and reserves the more elaborate, expensive tests for chemicals selected based upon expected human exposure (volume and dose), chemical structure relationship to known toxins, or positive results in the initial screening tests. In practice, the number of chemicals regulated by EPA under the Toxic Substances

Control Act (TSCA), is so large (new chemical entities introduced each year is estimated to be 1500) that only 10-20% of the TSCA mandated premanufacture notices (PMNs) receive a detailed review for potential adverse health or environmental effects. Since PMN's are rarely submitted with toxicity data, most evaluation is based upon a new chemical's structural relationship to existing chemicals and extrapolations from known toxic properties of well-characterized chemical classes. While structure-activity relationships are relatively well defined for some toxic responses, others (including neurotoxicity) are not well characterized and therefore the existing approach is much less reliable. Rapid screening tests are available for only a few parameters of toxicity.

IMPORTANCE OF RISK ASSESSMENT BASED UPON ORGAN SYSTEM TOXICITY

Part of the problem is that concerns about carcinogenicity have dominated discussions about the risks posed by toxic substances. However, the adverse effects on organs and organ systems (the nervous system, liver, immune system, cardiovascular system, and so on) may pose an equal or greater threat to public health. Consequently, it is important to devise risk assessment strategies to address noncancer health risks. However, whether it is advisable to tackle these organ systems, such as the nervous system, individually, is a question that should be addressed. Many of the aspects of toxicity testing, risk assessment and risk management which potentially need legislative attention are applicable across the spectrum of adverse human health effects. For this reason, this testimony will make little distinction between neurotoxic effects and non-neurotoxic effects.

The underlying thesis of this discussion is that additional toxicity testing of substances is required in order to protect our population from adverse health effects which contribute substantively to serious disease. The problem is most acute in the following areas: consumer products such as cosmetics, chemicals to which consumers and/or workers are exposed, and chemicals present in air and water. A major rationale for focusing on these particular areas of concern is that people are chronically exposed to potentially toxic chemicals under these circumstances. Toxicity tests of these types of chemicals, particularly new chemicals, with protocols employing chronic exposure are not common. While

considerable information is available as to the toxicity of some existing chemicals such as chlorinated hydrocarbons in the drinking water, the information on toxicity of newer environmental and occupational chemicals is truly pathetic. The problems associated with risk assessment of even relatively well studied environmental pollutants such as the chlorinated hydrocarbons, are grave, but pale in comparison to the dilemmas created by the paucity of toxicity testing of newer chemicals.

IMPORTANCE OF DETERMINING ADVERSE EFFECTS FROM CHRONIC EXPOSURE TO POTENTIALLY TOXIC CHEMICALS: DISTINCTION BETWEEN ACUTE TOXICITY AND CHRONIC TOXICITY.

One of the dogmas of toxicology is that the biological effects of a chemical administered chronically, for example for 6 months to 1 year, are often very different from the effects due to the same chemical encountered for a short time, perhaps just a single exposure. That is, the effects can be qualitatively as well as quantitatively different. This phenomenon frequently reflects the evoked disease process itself and examples of common chronic toxic manifestations would be peripheral neuropathy (degenerated peripheral nerves) and cirrhosis of the liver. Nitrous oxide, a very safe analgesic gas used routinely as an adjunct to surgical anesthesia, causes peripheral neuropathy when it is habitually abused. Ethanol has many adverse effects on both the nervous system and the liver, but cirrhosis is only observed in chronic alcoholics.

The point is that we have very few simple tests for assessing chronic toxicity. For the most part, we must conduct tests in which the substance is actually administered chronically to appropriately chosen laboratory animals. Such studies are the most costly in terms of resources. However, with our current scientific knowledge base, these studies are essential when there is reason to suspect chronic toxicity, based upon structure-activity relationships, pharmacological activity, and type of exposure. This is particularly true with substances which are potential neurotoxins since several extremely important manifestations of neurotoxicity will only be discovered in subchronic or chronic toxicity studies. This would include behavioral effects, and developmental neurotoxicity. Pesticides, which commonly have neurotoxic potential, should be tested by such procedures. In my opinion, the inclusion of such tests in specific circumstances, as indicated previously, is more critical than

requiring additional gross tests for neurotoxicity (e.g. the EPA's Functional Observational Battery) since some indication of such effects should be apparent in a routine toxicology test. It is the more chronic manifestations of neurotoxicity which are totally lacking in general toxicity testing paradigms.

HOW TO GET MORE TOXICITY INFORMATION WITHOUT JEOPARDIZING TECHNOLOGICAL ADVANCEMENT

The Critical Role of Industry.

When one considers the scarcity of data available for regulating new substances under the auspices of TSCA, it is apparent that many decisions are based upon factors other than its potential to cause adverse human health effects. The OTA report on neurotoxicity points out that "critics of EPA argue that regulatory resource considerations and a desire not to burden industry, rather than presumptive risk, are in fact driving chemical review criteria. They raise the question of whether the minimal screening given to the majority of chemicals is adequate to deal with high-risk chemicals that are not members of known risk categories." Lave and Upton (1987) have written that "there is reason to be concerned that requiring expensive, time-consuming testing would lower the rate of introducing new chemicals and slow innovation. However, a better balance is needed between protection and innovation."

TSCA puts the burden on the EPA rather than on industry. EPA cannot require toxicity data unless it finds in its initial review that a chemical may or will present unreasonable risks. Industry needs to become a more active participant in the review process.

An intriguing suggestion enumerated in the OTA report is that "Congress may...wish to request that EPA consider novel approaches to obtaining more extensive data from industry under TSCA, perhaps through the use of economic incentives." It is not realistic or desirable to mandate more extensive testing for ALL chemicals, regardless of intended use, or scientifically determined potentially for toxicity. However, industry should at least provide EPA with well documented reasoning as to why detailed toxicity testing is not needed. This could then be reviewed by EPA, who should have the authority to either concur or require testing. In this way, EPA would play a more familiar role as reviewer of industry-generated information rather than initiating the testing process. Such a role is more consistent with activities under licensing laws, in which the agencies review

industry-generated toxicity data. It is expected that this process will require more chemicals to undergo toxicity tests. How this is accomplished without burdening industry needs to be discussed. A task force with members from EPA, industry and academia might be convened to identify ways to implement such a process.

An additional way in which industry can aid in the regulatory process is to release more information to the public instead of secluding it under confidentiality provisions. The negative aspects of this practice are excellently described in the OTA report. They include: presentation of a significant barrier to efficient regulation since information cannot be shared between agencies; interference with research efforts to, for example, predict toxicity from structure activity relationships and develop new testing procedures; prohibiting solicitation of expert advice or consensus opinion; prohibiting public interest groups and scientists from information which would allow them to critique the regulatory agencies action on toxic substances. The Option for Congressional action detailed in the OTA report is excellent. It states: "Require that EPA and other Federal agencies revise the confidential business information provisions of various toxic substances control laws and regulations to allow greater access to toxicological information." While the details of how to provide industry with essential confidentiality need to be specified, society cannot afford to lose so much information when the need for knowledge is so great.

Improved Coordination of Federal Research and Regulatory Programs related to Toxicology

One of the Issues identified by the OTA study on Neurotoxicity was coordination of various programs related to toxicology. This issue has two aspects. One is coordination of interagency regulatory activities and the other is interfacing agency regulatory programs with research activities occurring throughout government, industry and academia.

Coordination of Interagency Regulatory Activities.

Recently, the Interagency Committee on Neurotoxicology was established. If this group, and additional groups covering other aspects of toxicology, were formalized by congressional mandate, it would help to ensure maximum use of U.S. regulatory resources. Given the seriously limited resources, this is a key action. In particular, it is critical for agencies reviewing the same chemicals, but different conditions of exposure, to formally

communicate and coordinate their efforts. The most obvious example is the importance of a close working relationship between EPA and the Occupational Safety and Health Administration (OSHA). Presently, standards for the same or similar chemicals are usually set independently by the agencies. A public interagency database would be very useful to avoid duplication of efforts not only between agencies, but between regulatory agencies and the scientific research community.

Interdependence of Regulatory Activities and Research Activities.

The risk associated with toxic chemical exposure is basically a scientific question. Until we gain a better understanding of the science, there is no hope of settling a host of difficult, controversial issues. Government regulation and research in toxicology and toxicology mechanisms are inextricably linked. Regulators must rely on scientific principles and research data in reaching decisions, but regulatory programs have provided the impetus for improvements in research methodologies and stimulated the conduct of many human and animal studies. Federal regulatory agencies have traditionally supported both intramural and extramural research programs. However, other Federal agencies, particularly the National Institutes of Health, have health-related research as their primary focus and mission. How much research regulatory agencies should support, especially intramural research, and how much should be the responsibility of research institutions, is a complex question which has not adequately been addressed.

How much research should Federal regulatory agencies support?

My impression from discussions with colleagues is that a perception exists within the scientific community that some regulatory agencies are so involved with conducting and sponsoring basic research that their regulatory obligations and conduct of research specifically directed toward regulatory issues becomes of secondary importance. An extension of this perception is that such research programs, for example some programs within EPA, are in competition with research efforts in institutions such as the National Institute of Environmental Health Science (NIEHS). In other words, there may be too much duplication of effort, in some programs, between NIEHS and EPA. Also, there may be a blurring of the mission of EPA as a regulatory agency as a result of too much attention to conduct of basic research. Whether EPA, and other regulatory agencies, should be mandated to further develop working

relationships with research organizations, needs further discussion.

This situation in Federal agencies is not unlike the dilemma that industry encounters when it considers whether to conduct research and development within the company, extramural by specific contract/agreement, or by collaboration with scientists in research organizations such as universities. From my own experience in industry, both scientists and administrators would ideally like to do all research and development within the company. This is primarily because the company has total control and confidentiality. The least control exists when the company depends upon research collaboration. There can be, however, great benefit derived from such collaboration. The company has access to the world's best scientists in any particular research field, but it does not have to establish and maintain a long-term commitment to either the scientists or the research field. By analogy, EPA, for example, might benefit enormously by establishing further collaborations with NIEHS rather than continued expansion of its own extramural and intramural research programs. Would it conserve resources if NIEHS, for example were formally mandated to consider the needs of EPA in development of its programs?

What is the role of scientific advisory groups?

Regulatory decision making depends upon scientific information and input is commonly solicited from the scientific community. Scientific advisory committees review scientific information and prepare written documents which often express a consensus opinion. This expert advice is not always used in the ultimate decision. For example, the National Institute of Occupational Health and Safety (NIOSH) is required by law to recommend exposure limits for OSHA but OSHA has rarely used these recommendations. In my opinion, it should be mandatory for regulatory agencies to use the scientific data from such advisory groups in its decision making. While it is recognized that regulators must consider more than scientific information, and sometimes there is continued disagreement among scientists, it is a waste of limited resources for agency-solicited consensus opinions and opinions from research organizations such as NIOSH to be ignored.

CRITICAL IMPORTANCE OF BASIC RESEARCH ON MECHANISMS OF TOXICITY IN DEVELOPMENT OF TEST METHODS AND RISK ASSESSMENT

Even if all the world's scientists directed their attention to

toxicity testing by traditional methods, we would be unable to test the chemicals which are covered by existing legislation. In addition to improving chemical selection approaches, there is a critical need for new, more rapid, toxicity tests. If we accepted the necessity of conducting additional neurotoxicity tests, as implied in the OTA report, do we have the resources to cope with the added workload? New tests need to be developed which will be predictive of adverse effects on complex organ systems such as the nervous system. I think there is very little disagreement among scientists that development of short term in vitro toxicity tests has very high priority.

How will new test development be accomplished and what needs to be done to advance development at a faster pace? I think the ultimate answer lies in providing additional resources for basic research in order to improve the molecular basis of toxicity testing. The more we understand about the nervous system, for example, the more apparent possible rapid testing procedures will become. As we unravel the complexities of the nervous system, we may be able to devise very simple biochemical tests for such complicated parameters as behavior, motor coordination, and learning. If we know the initiating events, such tests should be able to predict chronic toxicity as well as acute toxicity. I believe that test development is seriously limited by our understanding, at a molecular level, of organ systems and disease process. Increasing resources for toxicity test development is not likely to be productive unless resources for basic research are concomitantly increased.

It may seem far-fetched to devise a simple procedure for something as complicated as learning. However, successful development of short term carcinogenicity tests illustrates that it can be done. Development of the "Ames" test, the most elementary in vitro "carcinogenicity" test was due to the convergence of several scientific facts. Two of them are: many carcinogens are also mutagens; many chemical carcinogens must be "activated" in the body, i.e. metabolized to short-lived substances which are the actual carcinogenic chemicals. As technology was developed for manipulating bacterial genetics and devising mutagenicity tests, it was possible to devise a system in which mutagenic chemicals can be detected in vitro by incorporating an "activating" enzyme system; this is the "Ames" test. Since its introduction in the 1970's, it has proven to be reasonably predictive of carcinogenic chemicals. If we could identify the biochemical events which make up the learning process, we should be able to model the process and identify appropriate biochemical markers which could be measured in

an in vitro test.

Clearly, basic research in neuroscience, for example, will not by itself lead to toxicity test development. Toxicologists conducting basic research, particularly on mechanisms, are needed to bridge the gap between the basic research and toxicology. In an assessment of needs for research in the environmental health sciences, a task force convened in 1984 under the aegis of the National Advisory Environmental Health Sciences Council, made the following recommendation. "Developments in cellular and molecular biology should be exploited as quickly as possible in research on the mechanisms of environmentally provoked disease." Another group of experts (Draggen et al, 1987) wrote that "in constructing quantitative risk assessment models, it becomes clear that the unknowns in risk assessment can only be satisfied by continued basic research on biochemical mechanisms." Additional resources for studies on mechanisms of toxicity are needed.

Manpower shortages in nearly all areas of toxicology are critical. The rapid decline in the availability of Federal research funds, particularly NIH funds, is having an enormous negative impact on all areas of science, including toxicology. While the actual amount of funds appropriated for NIH has continually increased, the percentage of approved grants that are funded has rapidly declined. A funding rate of approximately 10% is common among Institutes for investigator-initiated individual research grants. This low rate is very discouraging to senior principal investigators, it is devastating to junior scientists who are trying to establish a research career and it negatively affects graduate students who are making career choices. While it is recognized that limited financial resources creates a need for budgetary choices, it is inconsistent with our concern about toxic chemical exposure, that excellent research proposals are not being funded and scientists are abandoning research careers.

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